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UNILATERAL EXOPHTHALMOS

A CONSIDERATION OF SYMPTOM PATHOGENESIS

BY

J. M. VAN BUREN, J. L. POPPEN AND G. HORRAX

(From the Department of Neurosurgery, the Lahey Clinic, Boston, Mass.)

INTRODUCTION

ALTHOUGH exophthalmos and its attendant symptoms may at first glance be dismissed as merely an expression of a disproportion between the orbit and its contents, closer inquiry as to their mechanism leads one into a surprisingly devious and at times ill-defined pathway. Many studies of expanding lesions of the orbit, such as Ingall's (1953) based upon a large series of cases have concerned themselves primarily with the frequency of occurrence and the histological features of the neoplasms. It has, however, occurred to us that if these same lesions be considered as experimental intrusions upon the orbit, features of fundamental interest might be adduced from their study. Therefore, in the present review, attention has been focused upon the clinical and pathological features which seemed to be of basic importance for the understanding, as far at least as it may presently be possible, of the mechanism of production of unilateral exophthalmos and its attendant symptoms.

In all 86 cases of unilateral exophthalmos which form the basis of the present study, excepting those in which the exophthalmos was secondary to an intracranial vascular anomaly, orbital structures were exposed by a transcranial approach and removal of the orbital roof. This approach allowed not only verification of the nature of the lesion, but the wide exposure provided rather precise data on its position and extent. Since the lesions in the present series lay scattered between the orbit and the middle fossa, opportunity arose for observation of the effect of compression of vascular and neural structures at various levels in their course. Grouped in this fashion, the results produced by these lesions were at times unexpected and features appeared which were difficult to explain on the basis of present knowledge of anatomy and physiology.

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The type and general location of the lesions is indicated in Table I. Definitions of location for a table of this sort are necessarily arbitrary and are arranged as follows: (1) Intra-orbital—tumour within orbital fascia whether primary there or extending there by invasion from adjacent structures. (2) Orbital—involvement of the bony orbit without perforation of orbital fascia. A lesion in this position might obviously displace intra-orbital structures. (3) Retro-orbital—a lesion out of contact with the orbit posteriorly. Many lesions passed group barriers and are so indicated.

TABLE I.—THE LOCATION AND TYPE OF LESIONS CAUSING UNILATERAL EXOPHTHALMOS

Location	*No. of cases*		*Type of lesion*
No tumour found	9*		
Intra-orbital	17	3	glioma of optic nerve; 2 lymphoma; 2 sarcoma; 2 neurinoma; 1 cyst of optic nerve; 1 lymphangioma; 1 mixed tumour lacrimal gland; 1 conjunctival epithelial cyst; 1 metastatic carcinoma; 1 inflammation of lacrimal gland; 1 aneurysm of ophthalmic artery; 1 angioma
Intra-orbital and orbital	11	3	meningioma; 3 sarcoma; 3 fibrous dysplasia; 1 lymphangioma; 1 tuberculous osteomyelitis
Orbital	20	11	meningioma; 4 fibrous dysplasia; 2 osteoma; 2 mucocele; 1 epidermoid cyst
Orbital and retro-orbital	11	11	meningioma
Retro-orbital	16	10	intracavernous rupture of internal carotid artery aneurysm; 2 meningioma (middle fossa); 2 glioma of optic nerve; 2 extensive posterior cerebral angioma
Intra-orbital, orbital and retro-orbital	2	1	neurinoma; 1 malignant cylindroma
Total	86		

*One case with a negative orbital exploration proved on follow-up study to have a carcinoma of the antrum with extension to the orbit.

In the subsequent discussion no attempt has been made to present the literature and our findings separately. Indeed, it seemed more pertinent to do the reverse. However, the presentation has been divided into two major groups: I, Pathological Characteristics of Lesions Producing Unilateral Exophthalmos, and II, Clinical Characteristics of Lesions Producing Unilateral Exophthalmos.

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I. Pathological Characteristics of Lesions Producing Unilateral Exophthalmos

A. *Meningiomas.*—As early as 1902, Schmidt considered that meningiomas arose from the leptomeninges. The evidence in this regard has been summarized more recently by Penfield (1932) and is generally well accepted. It is, indeed, hard not to accept this thesis when the appearance of the well-known collections of arachnoidal cells in the leptomeninges is compared with the microscopic appearance of many meningiomas. These clusters of arachnoidal cells do occur in the arachnoidal membrane overlying the optic nerve as pointed out by Cone and MacMillan (1932) and Craig and Gogela (1949). Indeed, the latter authors have shown typical psammoma bodies within these clusters.

Despite these features, indisputable examples of primary meningiomas of the optic nerve are remarkably hard to find. In most instances the growth extends posteriorly along the optic nerve to the foramen. This has occasioned much discussion as to whether meningiomas may arise within the intravaginal space of the optic nerve or whether all may not simply represent an extension from an intracranial mass (cf. Verhoeff, 1932; Cushing and Eisenhardt, 1938). The latter relationship was recognized as early as 1902 when Byers reported two personal cases, at least one of which is an example of an intracranial meningioma producing its initial symptoms by an intra-orbital extension. He was also able to find several convincing examples in the earlier literature. The evidence regarding the point of origin of a meningioma of the optic nerve is particularly open to question when this evidence is derived solely from observations made during an approach through the anterior orbit. A likely example of a primary meningioma of the optic nerve with post-mortem verification has been provided by Shapland and Greenfield (1935), but it may be noted that a meningeal tumour was also present in the middle fossa on the same side. More recently Craig and Gogela (1949) have reported nine instances where the growth appeared to be primary upon the optic nerve from evidence furnished by a transcranial exposure of the orbit.

In addition to these nine tumours, Craig and Gogela (1949) report an interesting group of five intra-orbital meningiomas which did not arise from the optic nerve or from any obvious extension of a foramenal growth. Since they were unable to find arachnoidal clusters either free or accompanying the true nerves and vessels within the orbit, they suggested that the unattached intra-orbital meningiomas might arise from arachnoidal tufts which had grown through the dural layer of the optic nerve and so had come to lie completely free of the dura.

Although meningiomas were the commonest cause of exophthalmos in our group, accounting for 27 of the 86 cases, none appeared to be primary within the orbit.

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Within the central nervous system, the meningioma shows little if any tendency to diffusely infiltrate tissues of ectodermal origin, advancing instead by extending fleshy knobs and fingers behind a connective tissue covering. Its ability to follow natural planes of tissue cleavage, however, is exemplified in meningiomas arising at the optic foramen. These may extend anteriorly to form a thin sheath about the optic nerve. Indeed, the tumour cells may extend into the space about the central retinal vessels (Forrest, 1949), invade the optic disc (Coston, 1936) and, as in Verhoeff's case, spread laterally beneath the retina (Cushing and Eisenhardt, 1938). Coston (1936) points out that the meningioma may penetrate the dura and once free in tissues of mesodermal origin, the neoplasm may lack a capsule and infiltrate orbital fat and voluntary muscle (Hudson, 1912; Forrest, 1949). Fig. 1 is an example from our series of invasion of the connective tissue of the Gasserian ganglion by a tumour which primarily involved the cavernous sinus and extended along the first trigeminal division to the orbit.

The intracranial meningioma has been considered primarily a tumour of middle life and this appears to apply as well to examples of this tumour within the orbit. Cases in children do occur, however (Forrest, 1949), and both of Dandy's (1922) examples of collar-like growths surrounding the optic nerve at the optic foramen were in this age group.

The frequency of exophthalmos in meningiomas of the sphenoid ridge is attested by Cushing and Eisenhardt's series (exophthalmos in 34 of 53 examples), Poppen and Horrax's (1940) series (all of 10 pterional tumours) and Craig and Gogela's group (exophthalmos in 25 of 64 tumours). The latter authors noted this sign as well in 5 of 16 meningiomas of the basofrontal area and in 5 of 44 meningiomas of the sellar region.

With the exception of the case illustrated in fig. 1 with maximal involvement of the medial portion of the middle fossa, all of our 23 meningiomas causing exophthalmos had attachment in the region of the sphenoid ridge. Craig and Gogela (1949) ascribed proptosis in their group of sphenoid ridge tumours to the following, either alone or in combination: (1) Osteoma formation in the orbital roof; (2) bone destruction and entry of tumour into the orbit by this defect; (3) tumour entry through one of the normal foramina. It is not entirely clear what is meant by orbital roof. Our experience agrees with that of Eagleton (1935) and Cushing and Eisenhardt (1938) in that bony invasion of meningioma is exceptional in the thin marrow-free bony plate covering the central portion of the orbit although it may be very active in the surrounding thicker bone. Another feature responsible for exophthalmos may be blockage of the posterior venous drainage from the orbit by tumour encroaching upon the foramina. This aspect will be discussed more fully below.

The present series was reviewed with attention to features which might indicate preoperatively whether extension had occurred within the orbit.

No certain criteria were found in four cases with such extension. In two vision was lost. One of these had anterior extension about the optic nerve and the other had generalized spread throughout the posterior orbit. Of the remainder, one had a fixed pupil and diminished visual acuity secondary to a meningioma arising lateral to the intracranial portions of the optic nerve but extending into the orbit to lie below the nerve. The last instance had invasion of the muscles posteriorly and diminished visual acuity. Diminished visual acuity (9 cases) or the failure of an isolated extraocular muscle to function (usually limitation of upward gaze) was found to exist without actual orbital invasion at operation. In one instance, pressure from tumour invading the ethmoid sinuses appeared sufficient to cause weakness of the medial rectus muscle. It would thus appear that in many instances weakness of an extra-ocular muscle may result from simple mechanical distortion of the muscle and may be unrelated to interference with its neural mechanism.

Meningiomas of the intraorbital portion of the optic nerve are said to enlarge the optic foramen less frequently than gliomas (Cushing and Eisenhardt, 1938; Craig and Gogela, 1949). Even in instances of dumb-bell growths within the optic foramen, Dandy (1922) reported that the optic foramen may not be enlarged. The plain X-ray films, however, are much more helpful with meningiomas of the sphenoid ridge. Of our 25 examples (in one instance no data was presently available) 24 showed sufficient hyperostosis to permit the diagnosis from the plain X-rays.

In terms of cure, the infiltrative nature of the meningioma in muscle and orbital fat must be considered in the operative treatment. However, it was recognized early (Byers, 1902) that regrowth of these tumours after partial removal may be remarkably slow.

In our cases of meningioma, 18 had been seen during a period of five years or longer and 9 of these for ten years or more. Five secondary operations were carried out at intervals respectively of three, four, five, five, and eight years, and another operation was advised but refused at seven years. (One case was operated upon three times at five-year intervals.) Another patient with a known subtotal removal of the growth at operation was followed four and a half years without clinical evidence of recurrence. It has, therefore, become abundantly apparent that the "five-year cure" has little meaning with this type of meningioma. Likewise, a life history such as is seen in this group of tumours makes it difficult to evaluate the results of radiotherapy.

B. *Gliomas of the optic nerve.*—Hudson (1912) was apparently the first to thoroughly review the subject and to firmly establish the gliomatous nature of the intrinsic tumours of the optic nerve. Duke-Elder (1941) considers them to arise from uni- or bipolar spongioblasts, while Verhoeff (1932) holds their origin in doubt but is inclined to incriminate a derivative

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of the astrocyte. Davis' (1940) excellent monograph should be consulted for a detailed consideration of these tumours. Because, however, of their appearance largely in children and their remarkably benign course, one is inclined to agree with Hudson (1912) that they are indeed different from intracranial gliomas and to suspect that many, at least, may be hamartomatous in nature.

Verhoeff (1932) has divided the histologic structure of these tumours as variations of three tissue types: (1) Finely reticulated type without fibrils of consequence; (2) coarsely reticulated type with similar nuclei, coarse fibres and a tendency to cystic spaces; (3) coarsely fibrillated type with heavy fibrils, often spiral, with neuroglial cells between and at times a radial arrangement of cells about vessels and connective tissue septa. In the above classification, the vacuolization and cyst formation of some tumours (cf. Martin and Cushing, 1923; Hudson, 1912) sufficient to cause their classification as "myxomas" (Duke-Elder, 1941) is, perhaps, not sufficiently stressed. One of our five cases (fig. 2) appeared to be a rather extreme example of this myxomatous change.

In their mode of growth these tumours exhibit several curious and poorly explained features. There may be anterior extension of the growth to involve the optic nerve head (Wilson and Farmer, 1940; Davis, 1940; Verhoeff, 1932) and in one of our cases "papillœdema" persisted over a number of years following removal of the optic nerve and tumour may have been evidence of this type of extension. The tumours may penetrate the pia-arachnoid membrane (an unusual thing for a glioma to do) and grow freely in the subdural space and may even penetrate the dura (Verhoeff, 1932). The tendency for proliferation of the connective tissue septa and coverings of the optic nerve, has been commented upon by many authors since Hudson's report in 1912 (perhaps most recently by Forrest, 1949), and the marked thickening of the pia-arachnoid is apparent in our figure (fig. 2) (the dura lies outside the illustrated field). This combined proliferation of neuroglial and fibroglial elements of the nerve has been emphasized, particularly by Davis (1939, 1940), in cases of associated von Recklinghausen's neurofibromatosis and gliomas of the optic nerve. Its manner of apparent growth caused Verhoeff (1932) to postulate that these tumours do not advance by invading the original structure but rather by causing the pre-existing neuroglia in the vicinity to take on neoplastic characteristics.

The age of onset is generally stated to be within the first decade (Hudson, 1912, Verhoeff, 1932, Forrest, 1949). Two of our cases were 15 and 18 years respectively at the time of operation, but the third was 52 years of age and had had but a four to five-year history of visual loss.[1] Although

[1]This and the case of the 18-year-old girl were reported in detail by Posner and Horrax (1948).

the appearance of this tumour so late in life is certainly unusual, Hudson (1912) found 7 of 111 examples in which the patient's age was in the fourth to sixth decades.

Although Duke-Elder (1941) warns that fatal "intracranial complications" may follow incomplete removal of these tumours, he had apparently not encountered local recurrences and this benign behaviour is apparently general experience even when only part of the mass has been removed (e.g. Davis' case followed eight years and one of Posner and Horrax's (1948) followed twelve years).[1] Hudson (1912) was also unable to find evidence of recurrence and cited six examples followed from six to twenty-four years without regrowth. In many of these cases the removal was known to be incomplete. In 2 of our cases (aged 18 years and 52 years) with intracranial involvement of the optic nerve and chiasm only incomplete removal was carried out. These patients have remained well and without evidence of visual loss on the opposite side over a period of four and a half years and ten and one-third years respectively. It would thus seem justifiable to temporize with these tumours when radical extirpation would result in further disability to the patient.

C. *Neurinoma.*—Although there is general agreement on the histology of this tumour, much has been written in the discussion of its origin. Features supporting a mesenchymal origin may be found in Penfield's (1932) chapter while those favouring a neurilemmal or Schwann cell origin will be found in the beautifully illustrated papers by Masson (1932, 1942). One may agree with Bailey and Herrmann (1938) when they express regret in the lack of a specific stain for the Schwann cell which would allow its unequivocal identification.

Much of the discussion has centred upon the origin of the connective tissue fibres, both collagenous and argentophil, which are found both about normal nerve fibres and within tumours arising from nerves. Those of the fibroblastic school cite this as confirming the mesenchymal origin, while those taking the opposite view contend that collagen is not formed within a cell and that reticulin fibres appear about the neurilemmal sheath of the nerve without relation to the endoneurial framework.

Boyd (1943) has, perhaps wisely, abstained from the discussion and draws attention to two papers in the *American Journal of Pathology* (1940). One by Tarlov proves by special silver techniques that only fibroblasts are present in neurinomas while Murray and Stout prove by tissue culture methods that the cell of origin is the Schwann cell. Indeed, Willis (1948) indicates that even an experienced pathologist may at times hesitate in separating fibromas from neurinomas and suggests that careful examination of fibromas may indicate that many arise from nerves! Therefore, we have continued Verocay's term "neurinoma." Although this is

[1]One of these still living and well at present, twenty-one years after operation.

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etymologically unsatisfactory, it is at least sufficiently non-committal to reflect the general uncertainty as to the cell of origin.

The histology of these tumours is too well described in the above articles to bear repetition here. The three tumours in the present series appeared the same. One is shown in fig. 3 and the heavy collagenous framework is to be noted. As Forrest (1949) has shown, however, the typical gamut of neurinoma histology, including the dense streaming or palisading pattern of Antoni type A tissue, the reticular œdematous Antoni type B tissue and the Verocay bodies may appear as in neurinomas elsewhere in the body.

In one of our cases, extension of the tumour through the orbital roof had occurred with a mass indenting the frontal lobe on the opposite side and surrounding the internal carotid and middle cerebral arteries of the same side. Standal (1950) also cites cases of intracranial spread after erosion of the orbital roof. That this need not be accompanied by histologic evidence of malignancy is illustrated in fig. 3 and in two of Standal's examples.

In terms of prognosis, our cases are of little aid. Standal reports an instance of partial removal without recurrence after ten years and another patient after removal of only a minor part of the tumour was followed three and a half years without evidence of enlargement of the mass. A benign behaviour would seem in harmony with their histologic structure.

D. *Benign mesenchymal tumours.*—7 cases in the present series were included in this group (2 osteomas, 3 hæmangiomas, 2 lymphangiomas).

In the surveys of Reese (1941) and Forrest (1949), hæmangiomas have proved to be the commonest primary orbital tumour accounting for 49 tumours in their combined total of 293 orbital tumours of all types. It may be noted, however, that of these 49 tumours only 32 were accompanied by exophthalmos. This appeared to be due to the anterior position of many of these lesions.

There is general acceptance of the thesis that the great majority of angiomatous tumours (both lymph and blood vessel) are of the nature of malformations or hamartomas rather than neoplasms (Boyd, 1943; Willis, 1948; Anderson, 1953). This receives support not only from the histologic appearance and the follow-up study of these lesions, but also from the youth of most of the patients. Reese found an average age in his 25 cases of 25 years, while 11 of Forrest's 24 examples were under 3 years of age.

Two of our cases have been classified as lymphangiomas rather than hæmangiomas on the basis that the endothelial lined tubules were filled with a protein containing fluid rather than red cells. Both were in children aged 4½ years and 7 years respectively. These lesions, although Schopfer reported 2 cases in children, are apparently infrequent; none were mentioned by Forrest (1949) and but one in Reese's (1941) series.

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From a clinical viewpoint Walsh (1947) reports that hæmangiomas frequently lie within the muscle cone producing proptosis without transverse displacement. In the present cases, however, both lymphangiomas lay in the superior portion of the orbit, and one extended upward to underlie the frontal and parietal scalp. Both Reese (1941) and Teitgen and Benedict (1951) note that angiomas of the cavernous type may be a cause on intermittent exophthalmos.

Although Benedict and Love (1939) note hyperostosis in a case of cavernous hæmangioma of the orbit, this is most unusual and their commonest sign by X-ray examination consists in thinning and concavity of the orbital walls as evidence of increased intraorbital pressure (Pfeiffer, 1943).

In most instances at operation the tumour is found to be discrete, encapsulated and easily separable from the surrounding structures. However, the variations in morphology so well illustrated by Forrest should be borne in mind as well as the rare malignant neoplasm of blood vessel origin. The rapid sclerosis and shrinkage of these endothelial tumours by X-ray radiation is well appreciated generally.

The 2 osteomas in our series were of the frontal sinus with secondary entry into the superior portion of the orbit. As Walsh (1947) points out, this is the commonest site of origin, with the ethmoid sinuses being next in frequency. Harrison's case (1942) occurred in a 15-year-old girl and apparently arose from the tuberculum sellæ resulting in blindness and optic atrophy. The lesion, although appearing densely calcified by X-ray, was not otherwise verified. Cushing (1927) has reported the intracranial complications of orbito-ethmoidal osteomata and pointed out that hyperostosis appearing in the medial portion of the orbit by X-ray favoured an osteoma in as much as most meningiomas lay laterally. Despite their quiescent histologic appearance, Walsh (1947) cautions that incomplete removal is apt to be followed by recurrence.

E. *Fibrous dysplasia.*—Fibrous dysplasia of bone has been defined by Lichtenstein and Jaffe (1942) as "a condition affecting one, several or many bones, the graver cases of which may present abnormal pigmentation of the skin, premature sexual development, hyperthyroidism or still other extraskeletal abnormalities." Microscopically the involved bone shows invasion by fibrous connective tissue which may on occasion exhibit myxomatous degeneration, and rarely small fluid filled cysts with bony or cartilaginous metaplasia. Blood vessels are usually sparse, though when present may be large and thin walled. Giant cells and occasional lipoid-filled cells are present. They point out that the latter do not argue for Hand-Schuller-Christian's disease because of their relative unimportance. They report that the disease is not related to hyperparathyroidism.

Involvement of the skull is relatively uncommon, but in his report of 8 cases of the polyostotic form, Lichtenstein (1938) cited an instance with

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lesions in the femur, tibia, pubis, ischium and skull with slight exophthalmos. Other instances of the polyostotic form associated with involvement of the orbit have been given by Etter and Hurst (1943) and Pugh (1945).

Schlumberger (1946) has reported 67 cases of the monostotic form of fibrous dysplasia with one instance of orbital involvement in a 21-year-old male. This patient complained of seven months of intermittent headache and downward displacement of the left eye. In Schlumberger's description of the microscopic features, he noted, in addition to the features cited by Lichtenstein and Jaffe (1942), the tendency for the new bone arising within the lesion to form a circle about an area of œdematous connective tissue (a feature shown in fig. 4). In addition, he reported the appearance of osteoblasts, though he found the areas of cartilage described by Lichtenstein and Jaffe (1942) only in conjunction with healing fractures.

Thus fibrous dysplasia, although presenting a well-defined microscopic picture, presents an array of clinical features which run the gamut from single slowly enlarging bone lesions to a widespread crippling disease associated with endocrine abnormalities. One is inclined to agree with Schlumberger's (1946) suspicion that this picture is a response of bone which may be elicited by any one of a variety of apparently unknown stimuli.

In view of the finding of 7 cases presenting as the monostotic form of fibrous dysplasia in the present series of 86 cases, it seemed curious that so little mention of it has been made in previous reports of orbital tumours. Pfeiffer (1943) referred to one case of "osteitis fibrosa cystica" among 200 cases of exophthalmos which may represent another instance of this lesion.

As Schlumberger (1946) points out, the lesions are frequently classified under other titles and indeed with the presence of foam cells the dividing line between this and xanthomatosis may prove a point for discussion. One may speculate whether some, at least, of Dandy's (1941) cases of Schuller-Christian's disease may not have been in this category as in only one of the 5 cases was there evidence of generalized xanthomatous deposits. The photomicrograph of the sections in one instance (Case 10, p. 65) would appear to be a granuloma (pseudotumour). In the remaining 3 cases lacking evidence of generalized xanthomatosis, the microscopic picture consisted in fibrous connective tissue, often appearing degenerated, collections of mononuclear cells and eosinophiles, foam cells, and in two instances giant cells were found. In only one case were bony spicules reported.

F. *Malignant mesenchymal tumours.*—Among the 8 cases of malignant mesenchymal tumours producing exophthalmos, 3 were undifferentiated sarcomas (1 of these possibly of striated muscle origin), 1 osteogenic sarcoma, 1 neurofibrosarcoma and 3 lymphomas. The relative frequency of these lesions may be noted in Forrest's and Reese's large series.

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Post-operative study in the 3 undifferentiated sarcomas showed death in the immediate post-operative period in one and the second could not be followed a significant period. The third was an "undifferentiated malignant tumour" in the orbit of a 14-year-old girl. X-ray treatment was given following orbital decompression. For over two years no recurrence has been evident. The osteogenic sarcoma widely invaded the skull and caused death in four years despite 4 decompressive procedures. The neurofibrosarcoma recurred and the patient died nine months after operation and but fifteen months from the onset of symptoms. Follow-up of lymphoma cases proved slightly more hopeful. Two patients who received post-operative radiation therapy have been followed two years and five and a half years respectively without recurrence. The third was operated upon too recently for consideration. Hine (1942) cites a similar experience of the good response of orbital lymphomas to radiotherapy.

G. *Miscellaneous tumours.*—This rather heterogenous group was composed of 1 malignant cylindroma of the sphenoid sinus, 1 tumour of the lacrimal gland considered of low malignancy, 1 conjunctival epithelial cyst, 1 epidermoid cyst, 2 mucoceles of the frontal sinus, and 1 metastatic carcinoma.

Follow-up of significant duration was obtained only in the case of the epidermoid cyst (ten years) and the tumour of the lacrimal gland (six and a half years). Neither had evidence of recurrence. The malignant cylindroma proved very invasive at operation and death occurred from coronary insufficiency three weeks later. At autopsy the growth appeared to arise in the sphenoid sinus, destroyed the entire medial sphenoid bone with extension into the nasopharynx, right orbit and antrum with less massive invasion of the left orbit.[1]

Three tumours in the present group had been initially reported as cholesteatomas. On reviewing the sections it became apparent that although all contained cholesterol slits at some point in the sections the lesions were quite different. One contained giant cells, reactive bone formation and fibrous connective tissue. The second was a cyst lined by squamous epithelium with a few sebaceous glands. The third proved to be a conjunctival epithelial cyst. In consequence the tumours were reassigned. Constans (1943) has used the term cholesteatoma to indicate a structure (1) lacking in an inflammatory wall, (2) located subperiosteally in the orbit, (3) containing or being composed of cholesterol. On reviewing his paper one becomes curious as to whether the term epidermoid cyst would not cover the same lesions in a less ambiguous manner. The subject of dermoid and epidermoid tumours of the orbit has been more recently reviewed by Pfeiffer and Nicholl (1948) with particular attention to the radiographic and pathologic features.

[1]Fig. 6 illustrates the rather striking perineural extension of this tumour in the posterior orbit.

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TABLE II.—SUMMARY OF FINDINGS IN NEGATIVE EXPLORATIONS

Case No. Sex Age	*Symptoms and general examination*	*Exophthalmos and local examination*	*Fundus*	*Visual acuity visual field*	*Cranial nerves III, IV, and VI*	*X-rays*	*Follow-up*
23 M 33 yrs.	2 mo. blurred vision OS, left headaches. 6 wk. diplopia and proptosis OS BP 200/110	3 mm.—not reducible	2–3D disc elevation OS	OS 20/50, OD 20/40 VF show inferior and especially inferior-nasal constric. OS	OS diverges laterally on upward gaze	Erosion medial left petrous ridge [*sic*]	1 mo. vision OS reduced to light perception
34 M 55 yrs.	6 mo. proptosis, epiphoria, blurred vision OD. BP 150/85 ? mass palpable in medial superior orbit	3 mm. OT increased to palpation. Conjunctival injection	Normal	OD 20/40, OS 20/20 VF by chart show upper temporal defect OD	Intact	Skull and sinuses normal	2 mo. 2 mm. proptosis*
36 F 37 yrs.	2 mo. proptosis OD and facial pain. BP 120/80, BMR −25 and −12. Serum cholesterol 182 mg.%	4 mm.	Normal	VA and VF grossly intact	Intact	Skull normal	2 yrs. no proptosis. 7¾ yrs. letter reports general good health, normal B.P. "My vision is not really impaired"
41 M 67 yrs.	3 mo. blurred vision OS, 2 mo. proptosis OS, 1 mo. diplopia and supra-orbital aching. BP 190/100	5 mm. Pressure on eye caused crackling like air in tissues	Normal	OS 20/20 OD 20/20 VF full by chart	OS pupil enlarged but reactive. Gaze upward and lateral limited	Skull normal	9 mo. 1 mm. proptosis OS. 2 yrs. physician reports no recurrence of difficulty
43 M 65 yrs.	9 mo. variable proptosis OS. 4 mo. blurred vision OS BP 110/70 BMR −21	7 mm. Dilated conjunctival vessels. Cataract extraction OD	2–3D disc elevation venous distension OS	Poor central VA OS	OS pupil enlarged but reactive	Skull and art' gram normal	3 mo. no proptosis VA 20/20 OS. 6 yrs. pt. denies proptosis. Vision slowly improves—can read large print. "I have a tendency to high blood sugar"

49 F 49 yrs.	7 yrs. proptosis OD BP 160/100 cardiac apex 2 cm. outside mid-clavicular line	5 mm. reducible	? OD (cataract) OS normal	OS 20/20 VF full by chart	Intact	Skull and orbits normal	1 mo. 1 mm. proptosis OS 5 yrs. no complaint. 2 mm. proptosis OS. BP 152/80 on radixin. X-ray negative
51 F 55 yrs.	7 mo. ago episode of III n. palsy OS. 1 mo. blind OS. ? duration proptosis BP 210/110	6 mm.	2–3D disc elev. medially, venous distension OS	OS count fingers at $\frac{1}{2}$ meter OD 20/30 VF full by chart	OS pupil small and fixed. All EOM limited especially upward, inward and outward. Slight reaction to accommodation	Skull enceph. and bilat. carotid art' gram normal	1 mo. 4 mm. proptosis and EOM unimproved
55 F 69 yrs.	1 yr. proptosis and discomfort OS. BP 200/115. Obese, nodules left side of thyroid	6–7 mm. OT : 35 OS, 20 OD. Congested episcleral veins. Proptosis reducible	Vessels showed mod. sclerotic change	OD 6/7 OS 6/10 VF full by chart	Intact	Skull and orbits normal. Abnormal orbital vessel by art' gram	10 mo. 5 mm. enophthalmos. $2\frac{3}{4}$ yrs. same but drawing sensation in eye remains
56 F 47 yrs.	2 mo. proptosis blurred vision OS BP 180/100 with cardiac enlargement	7 mm. OT : 28 OS, 11 OD. Lid œdema, chemosis conjunctival injection	Engorged veins and hæmorrhage about disc OS	VF grossly full. OS counts fingers at 4 ft.	OS 2 mm. pupil irregular and faint direct light reaction consensual reaction intact	Skull neg. Abnormal orbital ? vein by art' gram	OS blind 3 mo. OT 45 OS. 6 mo. OS removed for pain and glaucoma. No neoplasm found

*Negative exploration 21.8.46. His wife reported that 4.3.47 a right orbital exenteration was done for a malignancy (type not reported). He returned to work 16.8.49 but developed paranoid delusions and in October 1949 received two electroshock treatments with benefit. In November 1949 bleeding recurred more frequently in the right orbital cavity and by April 1950 he had lost the sight in his left eye. He died June 2, 1950, and post-mortem examination disclosed a cancer of the maxillary sinus extending into the nose, the orbit, the anterior cranial cavity and there were bony metastases elsewhere in the body.

H. *Unilateral exophthalmos without tumour.*—The 9 cases summarized in Table II bring to consideration unilateral exophthalmos unassociated with acute trauma to the orbit or without evident intraorbital tumour or inflammatory process at the time of exploration.

In order that exophthalmos may exist, there must obviously be a disproportion between the orbital contents and their bony container. Although it would appear that much regarding the pathogenesis of this condition remains obscure, the following schema may be advanced for the purpose of discussion:

I. Relative smallness of the orbital cavity.
   (1) Congenital defects of the wall.
   (2) Acquired defects of the wall.
   (3) Distortion of orbital growth.
   (4) Abnormality of sympathetic innervation.

II. Relative increase in orbital contents.
   (1) Venous hypertension.
   (2) Endocrine dysfunction.
      (*a*) Hyperthyroidism.
      (*b*) Hypothyroidism and oversecretion of thyrotropic hormone.
   (3) Developmental enlargement of intraorbital structures (e.g. buphthalmos, unilateral myopia of high degree).
   (4) Exophthalmos of uncertain origin associated with hypertension and glaucoma.

I. *Relative Smallness of the Orbital Cavity*

The congenital absence of the bony roof or posterior wall of the orbit may be associated early with an obvious encephalocele or meningocele, or, as in Dandy's (1929) case of an orbital meningocele, show minor early signs with a later abrupt increase in exophthalmos. LeWald (1933) pointed out a feature evident in the radiographs of one of Moore's (1931) cases, namely that depression of the floor of the orbit as well as absence of the orbital roof frequently occurs. Bruwer and Kierland (1955) indicated further changes which include a deepening and anterior migration of the temporal fossa and a deformity of the sella which may accompany this anomaly. These features were apparent in Schüller's (1918, p. 262) earlier case but the evidence was clouded since the changes were considered as due to an intracranial lymphangioma although no direct evidence was offered.

This deformity of the orbit also appears with neurofibromatosis sufficiently often to suggest something more than a chance relationship (cf. Moore, 1931; Seaman and Furlow, 1954). Although the actual neurofibroma may be present within the abnormal orbit (Childe, 1931) the majority of cases fail to have an intra-orbital tumour.

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Post-traumatic orbital defects may cause exophthalmos at a time sufficiently distant from the original injury to occasion some confusion. The portions of the orbital roof most likely to be fractured are the thinnest portions and unfortunately it is this area which is the most difficult to visualize on the X-ray film. Gardner's (1948) case provides an example of this. A 26-year-old man had suffered a head injury thirteen months before with some ecchymosis about the left eye. There followed some ten months of progressive visual failure and exophthalmos on this side. A frontal craniotomy showed an encephalocele extending into the orbit. Subsequent ventriculography and suboccipital craniotomy disclosed a hæmangioblastoma of the cerebellum. It then became apparent that exophthalmos had been occasioned by a traumatic orbital defect and a rise in intracranial pressure. Verbiest's (1953) case had a rather similar mechanism.

In children, pressure upon the orbital walls from adjacent expanding lesions may apparently result in a true collapse of the bony cavity and consequent exophthalmos. Davidoff and Dyke (1938) and Pfeiffer (1943) cite examples of relapsing juvenile chronic subdural hæmatomas wherein the deformity of the lateral orbital wall, with its convexity inward, resulted in exophthalmos. In Pfeiffer's case this amounted to 5 mm. and was associated with an abducens palsy.

The possibility of exophthalmos resulting from sympathetic stimulation in man is generally doubted and the subject is reviewed in detail by Brunton (1949). In carnivora, the bony lateral wall of the orbit is replaced by a dense periorbital membrane containing smooth muscle fibres. These are collectively referred to as Muller's orbital muscle. These fibres are responsible for exophthalmos which results from stimulation of the sympathetic pathways. In man, however, Whitnall (1921) describes Muller's orbital muscle as follows: "It completely fills the inferior orbital fissure, and is narrow, but two or three millimetres deep, in the centre, and fan-shaped at the extremities where it spreads in a thin layer over the orbital floor . . . Anteriorly it is continuous, according to Charpy (1912) with the orbital expansion of the inferior oblique muscle, a relation which the writer has been unable to confirm; posteriorly it can be followed beneath the annulus of Zinn to the lower extremity of the superior orbital fissure and even up to the wall of the cavernous sinus; whilst inferiorly it is in contact with the fat of the pterygopalatine fossa (Hesser, 1913). Through it there pass only small venules and nerves; some of its fibres accompany the veins out of the orbit (Krauss, 1911), and the inferior ophthalmic vein is related to it beneath the annulus of Zinn. Like other vestigial structures, it shows much variation in size." Wolff (1951) considers the muscle only briefly in his text (p. 21) but concludes that the muscle is too small to act as a protruder of the eye in man and that any effect that its contraction might have in collapsing veins which pass through

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it would be negated by the degree of free venous anastomosis within the orbit.

Microscopically, however, (Russell, 1936; Brunton, 1938) smooth muscle fibres do appear anteriorly in the human periorbital membrane although their functional potentialities are open to question (*see* Brunton, 1949 for additional discussion). Labbé *et al.* (1931) report an instance of a patient with hyperthyroidism (BMR +60) in whom transient exophthalmos followed injection of 50 mg. of ephedrine. In another patient exophthalmos resulted from a similar dose of ephedrine ten minutes following an injection of 5 mg. of thyroxine. Unfortunately the degree of exophthalmos was not measured. The rapidity of the appearance of exophthalmos (if not confused with simple lid retraction) would suggest either a muscular or vascular basis for the response. It has apparently been general experience (cf. Naffziger, 1949 and Pochin, 1939) that electrical stimulation of the cervical sympathetic trunk in man does not produce exophthalmos. This agrees with our own observations, and the failure of bilateral cervical sympathectomy to benefit thyrotoxic exophthalmos (Poppen, 1944).

However, Foerster *et al.* (1936) report exophthalmos on stimulation of the superior cervical sympathetic ganglion in man and instances of voluntary propulsion of the eyeballs (cf. Walsh, 1947, p. 267) remind us that individual variations do exist.

II. Relative Increase in Orbital Contents

The venous drainage from the orbit (Spalteholtz, 1933) is accomplished by valveless channels of variable conformation. The superior ophthalmic vein lies in the superio-medial portion of the orbit, joins the nasofrontal vein anteriorly and the cavernous sinus posteriorly after passing through the superior orbital fissure. In its course it receives the anterior and posterior ethmoidal veins, the lacrimal and muscular veins and veins from the ocular bulb and eyelid. It sends a collateral to the inferior ophthalmic vein. The inferior ophthalmic vein is derived from sources anteriorly (tear sac, eyelids, etc.) then runs posteriorly in the inferior portion of the orbit. It divides, sending one branch through the superior orbital fissure to the cavernous sinus and the second through the inferior orbital fissure to join the ramus profundus of the anterior facial vein. In its course it receives branches from ocular muscles, globe and the above-mentioned anastomosis from the superior ophthalmic vein. With such free anastomosis especially anteriorly, where it is hard to conceive of occlusion by pressure, the production of proptosis by venous stasis seems puzzling.

The inadequacy of the anterior orbital venous drainage, however, is attested by the reports of non-inflammatory lesions about the cavernous sinus which produce ipsilateral proptosis. Pituitary adenomas causing exophthalmos have been cited by Spaeth (1937), Dixon (1941), Meadows

(1944) and Walsh (1947, p. 1171). Aneurysms about the circle of Willis may produce similar changes presumably by the same mechanism (Jefferson, 1937, Dixon, 1941).

The importance of venous hypertension, as produced by a different mechanism, may be seen in our two cases of large cerebral angiomas and the 10 instances of intracavernous rupture of an internal carotid aneurysm with ipsilateral exophthalmos. Since these lesions did not encroach upon the orbit or block the orbital veins as a local expanding process might do, the exophthalmos resulted from an increased flow of blood into the cavernous sinus with its attendant rise in the pressure in the ophthalmic veins.

Dixon (1941), in particular, has emphasized venous stasis as a common mechanism in unilateral proptosis and unilateral proptosis can be produced experimentally in dogs by this mechanism (Brunton, 1949). Dixon points out that in testing the exophthalmos for reducibility by digital pressure, the response may be delayed in instances of lesions of the middle fossa. In these, initial resistance may be felt, but then the globe will sink slowly to normal position. This phenomenon was considered as evidence of the emptying of blood or lymph from the orbit.

Exophthalmos is a well-known sign of hyperthyroidism and although it is usually thought of as bilateral exophthalmos, numerous examples with unilateral involvement may be cited (Brain, 1936; Covitz, 1941; Dinsmore and Ruedemann, 1941; Dixon, 1941; Ellett, 1941; Pfeiffer, 1943; Kisner and Mahorner, 1947; Bedrossin, 1951; Saltzman and Mellicker, 1951). Although exophthalmos usually subsides following thyroidectomy, persistence of this sign is fairly frequent, amounting to 21 per cent in Cattell's (1934) series and it is of interest that 1·1 per cent showed an increase in exophthalmos following operation.

The subject of hormone-induced exophthalmos is a complicated one and the application of experimental work to clinical problems is hampered by uncertainty as to the degree of purity of the hormone preparations used and uncertainty as to whether experimental and naturally occurring human exophthalmos are one and the same thing. Important references to the subject may be found in the recent reviews of Aterman (1954), Brain (1955) and Greene (1955).

Due to the uncertainty as to the identity of induced exophthalmos in lower animals and the naturally occurring human type, it is perhaps wise to separate evidence regarding the two types to avoid confusion and unwarranted assumptions. With regard to both categories the following questions may be posed for purposes of orientation.

(1) Is exophthalmos induced by the thyroid stimulating hormone (TSH) or a separate "exophthalmogenic hormone" lacking in thyroid stimulating properties?

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(2) Does this exophthalmogenic factor act alone or in conjunction with one or more synergistic factors?

(3) What is the role of secretion of the thyroid gland in exophthalmos of endocrine origin?

(4) What is the nature of the orbital tissue response which results in exophthalmos?

There is a voluminous and rather controversial literature regarding the experimental production of exophthalmos. It would be improper to present this background *in extenso* here so the subject has been severely but, it is hoped, not too unwisely pruned to permit visualization of some major points which seem currently acceptable.

Evidence has accumulated that the exophthalmogenic and thyrotrophic properties of crude anterior pituitary preparations are separable in some degree at least. Lambie (1939) using a purified but potent thyrotrophic extract was unable to produce experimental ocular protrusion by its administration. Dobyns (1946a) and Smelser and Ozanics (1954) found that the exophthalmos producing activity of various TSH preparations might vary without strict relationship to the thyrotrophic effects. The former also found the fractions causing increased metabolism, epithelial hyperplasia of the thyroid and exophthalmos to be independently variable. Jefferies (1949b) after iodination of pituitary extract noted that the thyroid stimulating properties were abolished but some exophthalmogenic activity remained. Dobyns and Steelman (1953) later demonstrated that the thyroid stimulating hormone and the exophthalmos producing hormone could be separated on the basis of differing solubility in trichloroacetic acid. Smelser and Ozanics (1954 and 1955) also came to speak of an exophthalmogenic factor apart from the thyroid stimulating fraction since they could induce exophthalmos by a combination of pituitary fractions containing gonadotropins, FSH, ACTH, prolactin and growth hormone although none of the preparations alone induced proptosis. In their later publication they point out that some of the procedures used to "separate" the exophthalmogenic factor might serve merely to separate an adrenal or some other potentiating factor from the TSH. A biologically pure form of thyroid stimulating hormone is obviously needed to settle the problem.

The occurrence of other bodily changes in animals made exophthalmic by the administration of the thyrotrophic fraction is important since it may signal the presence of ancillary agents. Marked changes in fat metabolism are reported (Dobyns, 1946*b*, *c;* Jefferies, 1949*a*, *b*, *c;* Franckson, 1950) as well as adrenal enlargement (Friedgood, 1934; Smelser, 1939; Aird, 1940). The latter feature raises the question whether, as mentioned above, this hypothetical contaminent could have adrenocortical function. Aterman (1954) demonstrated the synergy of cortisone and the thyroid stimulating fraction of anterior pituitary secretion in the production of

exophthalmos in guinea-pigs. Of those who earlier took the view that it was unlikely that cortisone or ACTH played a part in experimental proptosis (Aird, 1940, 1941; Jefferies, 1949*c;* Smelser and Ozanics, 1951) it is perhaps significant that Smelser and Ozanics (1954 and 1955) have recently confirmed the finding that cortisone and ACTH will enhance the degree of exophthalmos produced by anterior pituitary fractions.

The secretion of the thyroid gland itself appears to play a very definite role in experimental exophthalmos. The majority of investigators agree that removal of the thyroid enhances the degree of and/or the incidence of hormone induced exophthalmos (Marine, 1938; Marine and Rosen, 1933, 1936; Smelser, 1936, 1937, 1938; Paulson, 1939; Dobyns, 1945, 1946*a;* Ludwig *et al.*, 1950; Asboe-Hansen and Iversen, 1951) although Pochin (1944) and Jefferies (1949*a*) contend that if the difference in behaviour of the body weight in normal and thyroidectomized guinea-pigs be taken into account there is no significant difference in the degree of exophthalmos between the two groups. Aterman's (1954) observations have indicated that this disagreement may not be a serious one. He found that the maximal degree of exophthalmos obtained by administration of ACTH and TSH fraction initially was roughly the same regardless of whether the guinea-pig was thyroidectomized or not. However, later on the degree of proptosis in the intact animal would tend to decline with the same amount of cortisone. Removal of the hyperactive thyroid gland would result in an increase in exophthalmos to a maximal degree.

The mechanism of the inhibitory relationship between cortisone and thyroid secretion is by no means clear. Either could produce a deficit in the other in two ways. The production of secretion could suffer either by interference with secretory tissue directly or through inhibition of the anterior pituitary trophic hormone, or conversely, a relative deficit could result from raising body requirements so that the secretion available would fall below the need. The possibility that one could directly neutralize or destroy the other remains but there seems no evidence of this.

Hill *et al.* (1950) found evidence of an inhibition of TSH secretion by cortisone and ACTH. Wolfson *et al.* (1951) espoused the view that cortisone, inhibited the thyroid directly—"corticogenic hypothyroidism" —which therefore might result in an increased production of TSH by the adenohypophysis and exophthalmos. Aterman (1954), however, found this explanation untenable since his animals made exophthalmic with TSH fraction and cortisone showed no signs of thyroid inhibition and indeed tachycardia and thyroid hyperplasia occurred. He concluded that the rise in general body metabolism by thyroid secretion simply resulted in an increased utilization of adrenal steroids and prevented an effective synergy between cortisone and TSH. Removal of the thyroid gland thus lowered the body requirements for cortisone and permitted resumption of the TSH-cortisone exophthalmogenic activity.

The histologic basis for the exophthalmic response of guinea-pigs following administration of TSH is apparently an increased fluid (Pochin, 1944) fat and fibrous tissue content of the intraorbital tissues (Smelser, 1943). In this and a subsequent study (Smelser, 1949) it appeared that this reaction was the rather peculiar property of orbital fat inasmuch as fat from other areas transplanted to the orbit failed to show the increased fluid content under similar conditions. Dobyns (1946*b*, *c*) found polymorphonuclear cells and tissue macrophages loaded with tiny fat droplets early in the reaction. Later came an increase in new connective tissue.

In man evidence regarding the effect of the anterior pituitary fraction is very scanty. Stallard (1936) produced a marked exacerbation of exophthalmos in a case of exophthalmic ophthalmoplegia with a low BMR by the administration of a thyrotrophic fraction. Schrire (1948), however, did not produce exophthalmos in normal man by this means although question could be raised as to the adequacy of the dosage employed. Uncertainty as to the role of TSH in exophthalmos again arises since the blood and urine of patients with the severe form of ophthalmopathy in Graves' disease do not regularly show a high thyrotrophin titre (Purves and Griesbach, 1949).

The results of attempts at suppression of pituitary function in the treatment of exophthalmos have, on the whole, been favourably reported and so suggest some pituitary factor is responsible. Beierwaltes (1951) found pituitary irradiation beneficial in advancing exophthalmos as have Brain (1955) and Stallard (1955) although the latter suggested that the results were due to scatter radiation of orbital structures and so directed radiation primarily at the orbits. Albeaux-Fernet *et al.* (1955) report improvement in a severe case of exophthalmos associated with hyperthyroidism by surgical hypophysectomy.

The effect of cortisone and ACTH in man is uncertain. Chandler and Hartfall (1952) found cortisone to benefit exophthalmos while the results of a Medical Research Council investigation (Greene, 1955) indicated that the preparation had no apparent effect on exophthalmos.

The effects of administration of thyroid preparation although enthusiastically endorsed initially as a treatment for exophthalmos, particularly of the post-therapy type, has lately been regarded by most with scepticism (Greene, 1955). Curiously enough, exophthalmos has been reported to have been provoked in man by thyroid or thyroxin administration, thyroxin plus adrenalin or ephedrine and in non-exophthalmic cases of Graves' disease by ephedrine (cf. Brunton, 1949). Instances, however, in which actual measurements of ocular protrusion were not made are of doubtful value.

There appears to be sufficient evidence now to permit a separation of the pathological picture in exophthalmos associated with Graves' disease and that occurring spontaneously or in post-therapy states (exophthalmic

ophthalmoplegia, Brain, 1936; thyrotrophic exophthalmos, Mulvany, 1944; severe ophthalmic form of Graves' disease, Rundle and Wilson, 1944; hyperophthalmopathic Graves' disease, Means, 1948; malignant exophthalmos, Rundle *et al.*, 1953; severe infiltrative ophthalmopathy, Smelser, 1955).

In hyperthyroidism Rundle and Pochin (1944) present a well-controlled study of 17 patients both with and without exophthalmos. Their most important finding was a marked quantitative increase in the fat content of the orbit and the fat content of the extraocular muscles was doubled. Histologic examination alone has proved somewhat less rewarding. Friedenwald (1932) found abnormalities in only one of six cases of exophthalmic goitre. These consisted in marked atrophy and fibrosis of the extraocular muscles and many fibres were replaced by fat. Focal accumulations of lymphocytes were found in the interstitial tissues but no œdema. In an examination of a further six cases of Graves' disease (no definite statement was made as to the presence or absence of exophthalmos) Russell (1936) found pathologic changes in only one instance. These consisted in lymphorrhages in the extraocular muscles.

In exophthalmos unassociated with thyrotoxicosis, the changes in orbital structures have in general taken quite a different form. In a quantitative tissue assay, similar to their previous study, Rundle *et al.* (1953) found in a case of malignant exophthalmos without clinical or pathological evidence of thyroid hyperplasia, that there was enlargement of the extraocular muscles to two to five times their normal size. The increase was due to swelling of the fibres, increase of fibrous connective tissue and infiltration with lymphocytes and plasma cells. There was no evidence of fatty hypertrophy as in thyrotoxicosis. Muscular hypertrophy has also been reported by Burch (1929), Naffziger (1933) and Mulvany (1944) and an increase in fibrous tissue by these investigators and others (Merrill and Oaks, 1933). A very striking photograph of this muscular hypertrophy may be found on p. 374 of the *Trans.* Ophthal. Soc. of the United Kingdom 75 (1955).

The occurrence of exophthalmos associated with hypertension and cardiac disease has been noted briefly by Naffziger (1933). Spaeth (1937) also reported exophthalmos with hypertension and increased ocular pressure. He suggested that the ocular hypertension might be due to varicosities of the orbital vessels. The coincidence of glaucoma and endocrine exophthalmos has been noted by Ruedemann (1937) and Beierwaltes (1951). Brunton (1949) concluded that there could be little relationship between hypertension and exophthalmos.

In the present series nine explorations of the orbit for unilateral exophthalmos were performed without the discovery of a tumour or any other apparent cause. Case 34 (Table II) demonstrated that despite one's best attempts, it is possible to miss an intraorbital neoplasm even in face of the

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wide exposure of the orbit afforded by the transcranial approach. With this in mind the follow-up data on the remaining cases was approached in a critical fashion. In two cases, contact was possible only for one month following discharge from the hospital. In a third, due to the recentness of the operation, the follow-up has been less than a year. However, since the involved eye was removed in this interval because of blindness and pain from glaucoma and no abnormality of intraorbital structures was found at this time, the case seems an acceptable one. Of the remaining 5 cases, 2 were followed over two years and 3 between five and seven and three-quarter years without evidence of an expanding intraorbital process.

Of the 8 patients remaining in the series, 6 were hypertensive, 5 having a systolic pressure of 190 or over and a diastolic of 100 or more. In 2 of these cases the ocular tension was measured and found to be elevated. The remaining signs were considerably varied. 2 had measurable papill-œdema, while a third had engorged veins and hæmorrhages about the disc in the involved eye. In 2 vision was considerably decreased. One patient (Case 23) showed constriction of the visual field inferiorly (cf. fig. 3). Although the post-operative follow-up of this case is, unfortunately, short, an inferior quadrantic field defect had been previously reported (Poppen, 1944) in a patient with thyrotoxic exophthalmos. The mechanism in both these instances remains obscure. 3 had impairment of extraocular motion especially upward motion. Pupillary abnormality appeared in 4 of which 2 consisted in an enlarged but reactive pupil while the third demonstrated an irregular pupil contracting better to accommodation than to light. In the last case the pupil was small and fixed.

X-ray films failed to give certain positive information with the exception of the demonstration in 2 cases of an unusual intraorbital vessel on arteriography (figs. 7 and 8). In Case 56 (fig. 8), the large vessel was identified at operation in the superior medial portion of the orbit and biopsied. Microscopic examination proved it to be a vein.

The 2 remaining patients in this series of 8 were normotensive but showed a somewhat diminished metabolic rate.

In summing up these negative explorations, one may note the absence of a fixed dilated pupil or an extraocular muscle palsy suggestive of involvement of a single nerve. This, as will be shown, however, is a common finding in exophthalmos of demonstrable cause and forms no useful differential criterion. The presence of a large intraorbital vein filling during the arterial phase of arteriography would indicate an abnormal rapidity in orbital circulation although in the absence of a demonstrable hæmangioma, its mechanism is far from clear. Thus exophthalmos associated with hypertension and glaucoma or a low basal metabolic rate may suggest that the exophthalmos is due to a cause other than an intraorbital expanding lesion. However, such cannot be excluded

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FIG. 7.—Tracings of the arteriograms from Cases 56 (above) and 55 to indicate the unusual orbital vessel. In neither case was tumour found at operation.

with even reasonable certainty short of orbital exploration. Fortunately, this procedure offers the best hope of relieving the patient's symptoms, and at the same time affords the best opportunity for verifying the cause of the complaint.

II. CLINICAL CHARACTERISTICS OF LESIONS PRODUCING UNILATERAL EXOPHTHALMOS

A. *Changes in vision.*—Gliomatous infiltration of the optic nerve had occurred in 5 cases. In 2 the lesion was situated in the prechiasmal portion of the optic nerve and had in both cases reduced vision to the point where the field could not be charted. In one of the remaining, however, the tumour involved the optic nerve within the orbit and sufficient acuity remained to permit visual field examination by con-

frontation (Case 59). No defect was found. This general depression and constriction of the visual field has apparently been Traquaire's (1949) experience in gliomas of the optic nerve.

Of the remaining 43 cases associated with visual impairment, the lesions lay outside the dural sheath of the optic nerve. Visual acuity was insufficient to permit adequate visual field testing in 19 of these. Of the remaining cases, 3 had inadequate testing of the visual field, 8 showed scotomatous defects, while 13 showed either concentric constriction of the peripheral field (5 cases) or asymmetrical defects of the peripheral field (8 cases). The three instances of a central scotoma and five of the asymmetrical peripheral defects were associated with a visual acuity of 20/200 to 2/200. All the remaining cases charted had an acuity of 20/50 or better.

Although Traquaire (1949) mentioned wide sector depression of irregular outline and central or centrocæcal scotomas to result from pressure upon the optic nerve (noting in the latter instance that the peripheral depression may be minimal as in Case 44) an additional form of scotoma may be pointed out. This, as in Case 40 (fig. 9), consists in

TABLE III.—TYPE AND LOCATION OF LESIONS IN CASES IN WHICH VISUAL FIELD DEFECTS WERE CHARTED

Case	*Location*	*Lesion*
3	Orbital	Mucocele, frontal sinus
4	Orbital	Meningioma, sphenoid wing
7	Orbital and retro-orbital	Meningioma, sphenoid wing
12	Orbital and retro-orbital	Meningioma, sphenoid wing
13	Intra-orbital and orbital	Neurofibrosarcoma
14	Orbital	Meningioma, sphenoid wing
19	Orbital and retro-orbital	Meningioma, sphenoid wing
23	No tumour	
24	Orbital and retro-orbital	Meningioma, sphenoid wing
26	Orbital and retro-orbital	Meningioma, sphenoid wing
34	No tumour	
40	Orbital	Meningioma, sphenoid wing
44	Intra-orbital	Cyst of optic nerve
46	Retro-orbital	Meningioma, para- and supra-sellar
50	Intra-orbital and orbital	Fibrous dysplasia
58	Orbital	Fibrous dysplasia

a crescentic area of blindness centred upon the normal cæcal scotoma. Case 58 (fig. 9) may be an incomplete example. In both of these, pressure upon the optic nerve appeared to be in the region of the optic foramen. Lillie and Adson (1934) report a somewhat similar scotoma to result from callus formation about the optic foramen. However, in their 2 cases, the tips of the crescent had elongated and joined to form an annular scotoma and a central scotoma was present as well.

In the above cases, it would appear that the visual changes must rest

upon one or more of the following mechanisms: (1) Infiltration of the optic nerve; (2) Traction upon the optic nerve; (3) Compression of the optic nerve fibres, and (4) Impaired vascular supply to the optic nerve. The first may be decided on inspection. Consideration of Table III would suggest that moderate degrees of traction (up to 8 mm. of exophthalmos)

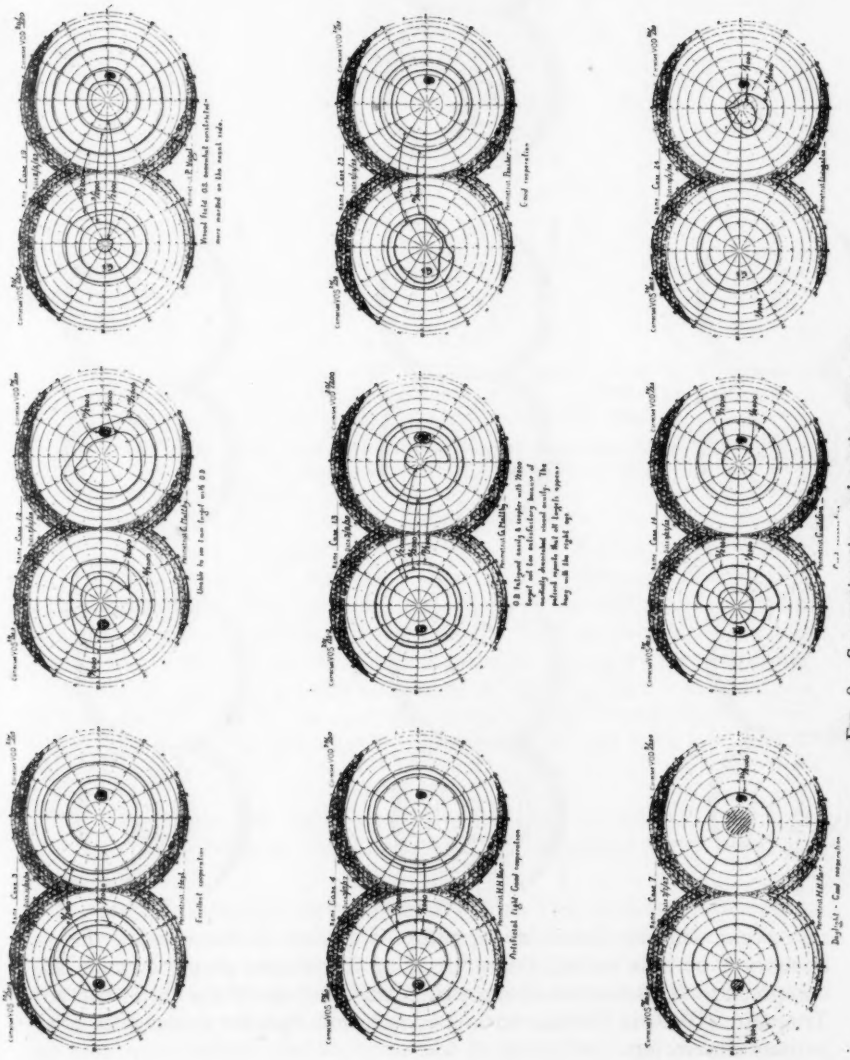

FIG. 9.—*See continuation and caption next page.*

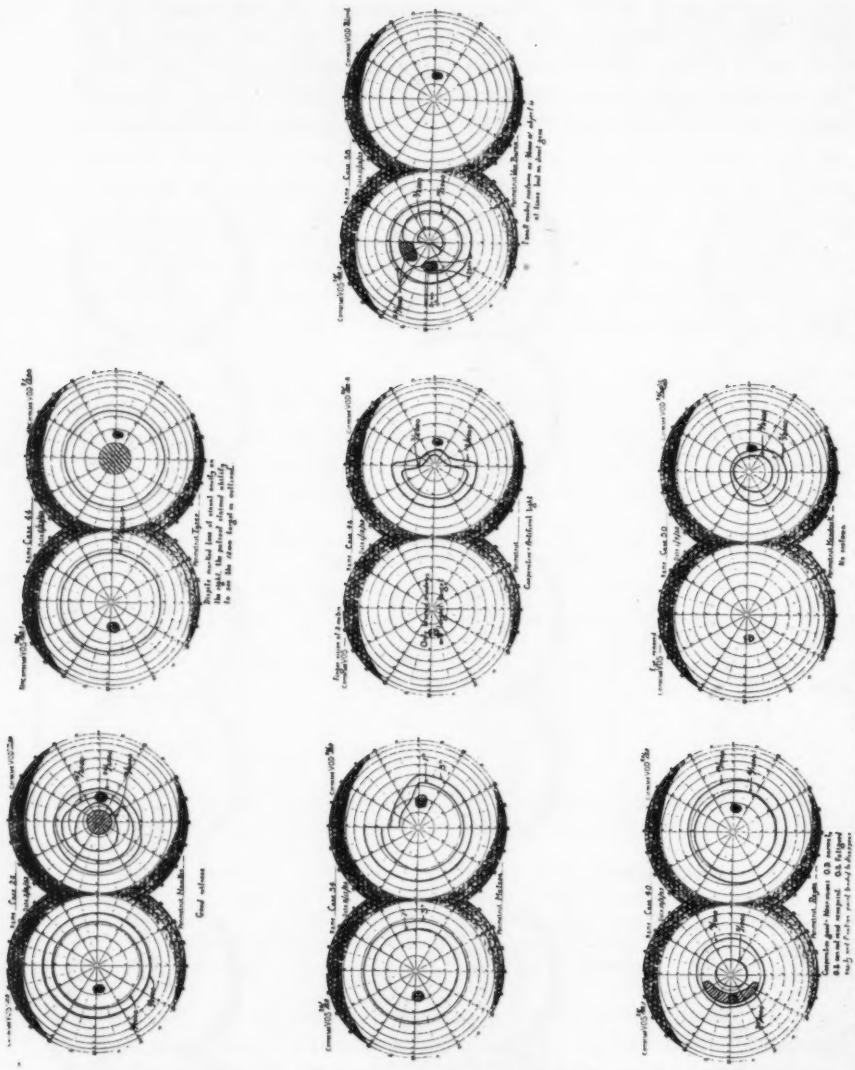

FIG. 9.—The types of visual field abnormality associated with lesions producing unilateral exophthalmos.

may occur without evident abnormality of vision. Unfortunately, there appears to be little to help one in deciding the relative preponderance of compression or ischæmia in impairing the function of the optic nerve. Traquaire (1949) is inclined to favour ischæmia but the evidence is not entirely convincing.

TABLE IV.—THE RELATIONSHIP BETWEEN VISION AND EXOPHTHALMOS

*Millimetres of exophthalmos**	*Patients with normal visual fields and acuity*	*Patients with abnormal visual fields and/or acuity*	
2	3	4	
3	3	4	
4	3	7	
5	8	5	
6	2	2	
7	2	7	
8	6	5	
9	1	2	
10	0	1	
12	1	0	
13	0	1	
14	0	1	
15	0	1	
19†	0	1	
Not measured	11	5	
	40	46	Total: 86

*Measurements made with a Hertel Exophthalmometer. The difference between the measurements of the exophthalmic and normal eye are taken as the millimetres of exophthalmos.

†The left eye had been enucleated. The actual measurements with a prosthesis in its place were: right 37 mm.; left 18 mm. with a baseline of 107 mm.

One is inclined to suspect that the apparently distinct types of visual field defects must have localizing significance. Although considerable time was spent in comparing the description of the lesion as recorded in the operative and radiologic notes and the field defect itself, no sound conclusion could be reached. This point is certainly one worthy of pursuit. In terms of present knowledge of the disposition and vascular supply of fibres within the optic nerve it is difficult to explain why peripheral, macular or intermediate fibres should bear the brunt of injury in a given instance.

B. *Changes in the optic papilla.*—In Tables V and VI some of the findings related to the appearance of the optic nerve head are summarized.

As one might expect, there appeared (Table V) a tendency to temporal separation between papillœdema and its preludes and optic atrophy with the separating point at roughly a year from the onset of exophthalmos. (In cases having a short duration of exophthalmos prior to the finding of optic atrophy, the earliest complaint had been visual loss.) The appearance of optic atrophy was accompanied by some degree of visual impair-

TABLE V.—THE RELATIONSHIP BETWEEN THE DURATION OF EXOPHTHALMOS, DEGREE OF EXOPHTHALMOS AND THE APPEARANCE OF THE OPTIC FUNDUS

Duration of exophthalmos	*Normal*	*Venous congestion*	*Blurred discs*	*Measurable papillœdema*	*Pallor of disc*	*Disc not visualized*	*Totals*
Under 1 mo.	8, 6, 2*, 5, ?	?, 8	7		3		9
Under 3 mo.	3, ?, 4, 5, 3, 4	13		3	5, 5, 4		11
Under 6 mo.	3, 5, 3, 8	5	?		7, 7, 4		9
Under 1 yr.	9, ?, ?, 7	8, 5, ?, 7	5	7	5, 8, 10, 4	?	15
Under 2 yrs.	4, 8, 3, 8	4	4		8, 2, 7, 5		10
Under 4 yrs.	5, 7				19		3
Under 8 yrs.	7	7			12, 2	5, ?	6
Over 8 yrs.	4	3			9, 14, 15, 4, 2	?	8
Uncertain Duration	?, 5, ?, ?, 2	?	8	?, 8, ?, 2, 6	8, 9	4	15
Totals	32,	12	5	7	25	5	86

*This case showed choroiditis near the papilla.

(Numbers refer to degree of exophthalmos in millimetres. In cases where this was not measured a ? is used.)

ment in all but one case while but 15 of 24 cases in the congestive group (venous engorgement to papillœdema) had any diminution in visual acuity.

In terms of location of the lesion (Table VI), it may be noted that intra-orbital lesions failed, in general, to give swelling of the nerve head. This would attest to the venous congestive basis of the swelling since it appeared more frequently with lesions about the posterior orbital foramina. The three instances of well-marked papillœdema in hypertensive patients in whom no tumour was found is interesting and possibly suggests a venous congestive basis for this syndrome. All of these cases point to the inadequacy of the anterior venous drainage from the orbit. In view of the text-book descriptions of valveless anastomoses between the ophthalmic venous system and the facial system, it is curious that compensatory dilatation

TABLE VI.—THE RELATIONSHIP BETWEEN THE APPEARANCE OF THE OPTIC FUNDUS AND THE LOCATION OF THE LESIONS

Location	*Normal*	*Venous congestion*	*Blurred discs*	*Measurable papillœdema*	*Pallor of disc*	*Disc not visualized*	*Totals*
No tumour found	4	1		3		1	9*
Intra-orbital	10		1		6		17
Intra-orbital and orbital	1	1		2	5	2	11
Orbital	10	3	1		6		20
Orbital and Retro-orbital	1	2	2	1	5		11
Retro-orbital	5	6	1	1	3		16
Intra-orbital, orbital and retro-orbital						2	2
Totals	31	13	5	7	25	5	86

*The case subsequently found to have a carcinoma of the antrum with orbital invasion had no abnormality of the optic fundus at the time of orbital decompression.

of these channels, which might reasonably be expected, seems insufficient to adequately drain the orbit.

C. *Changes in intraocular muscle function.*—A fixed dilated pupil occurred but four times in the present series. In 3 cases, it was associated with a massive lesion (1 meningioma, 1 neurofibrosarcoma, 1 malignant cylindroma) causing gross distortion of orbital and retro-orbital structures. In the fourth instance the lesion proved to be a meningioma which lay lateral to the left optic nerve and passed into the orbit to lie just below the optic nerve. This resulted in an inferior and medial deviation of the eye at rest and active motion to a limited degree was present in the planes of action of the superior and possibly the inferior oblique muscles. Sufficient obstruction to the retinal venous flow had occurred so that two to three dioptres of papillœdema was present. Thus it is curious that despite evidence of severe compression of structures of the orbital apex, that visual function had not grossly decreased and the visual fields were intact by confrontation.

Of more interest was the finding of a dilated pupil reacting to light in 9 cases (Table VII). (In one case a pupil in an amaurotic eye reacted consensually.) Review of the location of the lesions showed a rather uniform scattering (two intraorbital, four benign lesions of the orbit itself, one parasellar and suprasellar meningioma, two gliomas of the intracranial portion of the optic nerve and chiasma). Three additional examples occurred in the 9 cases of unilateral exophthalmos without evident neoplasm at operation. There seemed little connexion of the pupillary change with paralysis of the extraocular muscles, for aside from difficulty in elevation and lateral deviation of the globe in one instance of

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TABLE VII.—CASES PRESENTING AN ENLARGED PUPIL BUT WITH RETENTION OF THE LIGHT REFLEX ON THE SIDE OF THE LESION

Case	35	39	6	17
Pupil	dilated	dilated	dilated	sl. dilated
Light reflex	poor	—	—	sluggish
Muscle weakness	—	SR and LR	—	SR
Ptosis	—	—	—	slight
Visual acuity	2/200	—	—	20/70
Visual field	central scotoma	—	—	—
Exophthalmos	7 mm.	8 mm.	3 mm.	4 mm.

Lesion	sarcoma	mixed tumour	meningioma	fibrous dysplasia
Location	intra-orbital	intra-orbital	orbital	orbital

Case	30	46	2	18	63
Pupil	sl. dilated	dilated	sl. dilated	dilated	dilated
Light reflex	—	*	†	poor	sluggish‡
Muscle weakness	—	—	—	—	LR
Ptosis	—	—	—	—	—
Visual acuity	—	poor	blind	poor	blind
Visual field	—	????	—	????	—
Exophthalmos	5 mm.	not measured	9 mm.	2 mm.	4

Lesion	meningioma	meningioma	glioma	glioma	fibrous dysplasia
Location	orbital and retro-orbital	parasellar and suprasellar	optic nerve and chiasma	optic nerve and chiasma	intra-orbital orbital

*Case 46: The accommodation reflex was considerably brisker than the light reflex.
†Case 2: The pupil reacted consensually but not directly to light.
‡Case 63: The accommodation reflex was not elicited.

intraorbital tumour and of elevation of the globe in a second case with orbital involvement, no weakness of the extraocular muscles was found. The fact that lesions both within and without the optic nerve are represented should be noted.

One is tempted to suggest that the finding of an enlarged reactive pupil in the absence of extraocular muscle palsy is simply a spastic mydriasis due to sympathetic overaction. However, it appears that lesions of the third nerve proximal to its intracavernous course (i.e. in an area where simultaneous stimulation of sympathetic fibres would seem most unlikely, cf. Sunderland and Hughes, 1946) may produce this picture. In both clinical and experimental compression (Reid and Cone, 1939) of the oculomotor nerve, a dilatation of the pupil with retention of the light response is seen prior to the loss of the light response and recovery occurs in the reverse order.

The selective sensitivity of parasympathetic fibres may be based upon their superficial position. In man, as Sunderland and Hughes (1946) have

demonstrated, these fibres lie about the circumference of the nerve and particularly on its superior aspect where they would appear most exposed to injury. Walshe (1947, p. 197) reports an instance of an incomplete alcohol block of the oculomotor nerve in a monkey which resulted in a fixed dilated pupil without extraocular muscle weakness. This would likewise suggest a peripheral distribution of the pupilloconstrictor fibres.

In his discussion of symptom pathogenesis in orbital tumours, Duke-Elder (1952, p. 552) ascribes mydriasis to sympathetic stimulation and does not mention the possibility of partial parasympathetic inactivation. Since, however, partial inactivation does occur in third nerve lesions outside the orbit, it may not be unreasonable to suppose that pressure might act in a similar fashion when exerted on the peripheral continuations of the same fibres.

In 2 cases notation was made of relatively greater activity of pupillary constriction on convergence than on direct light exposure. Further research appears necessary in this direction but existing evidence may indicate a separation of fibres subserving the convergence and light responses of the pupil. It may be pointed out, however, that the peculiar ability of the muscular branches of the third nerve to successfully reinnervate the sphincter of the pupil may falsely give the impression of an anatomical separation of the accommodation and light reflex pathways, when in reality the explanation lies in an entirely different direction. Thus, following regeneration of fibres in the third nerve, Ford *et al.* (1941) observed various anomalies in pupillary function. These might consist in (1) persistence of a dilated totally unreactive pupil, (2) a pupil fixed to light but constricting on convergence or movements requiring third nerve participation, although the pupil might dilate on abduction of the eye, or (3) a pupil behaving as in 2, but showing a slowed light reflex of diminished amplitude.

Within the orbit, apparently good evidence exists that the accommodation and light responses of the pupil follow separate pathways in man (Nathan and Turner, 1942). In the higher primates, Foerster *et al.* (1936) demonstrated that removal of the ciliary ganglion resulted in a pupil fixed to light but constricting on accommodation. From Nathan and Turner's report, clinical instances of this syndrome are infrequent and none were noted in the present series.

D. *Changes in extraocular muscle function.*—Among the 26 instances of muscle palsy in the present series, weakness of the superior rectus muscle appeared twenty-one times. It was an isolated muscle weakness in 2 cases; accompanied by ptosis in 2 cases, accompanied by lateral rectus weakness in 3 cases; accompanied by medial rectus weakness in 2 cases and accompanied by varying degrees of impairment of all muscle actions in 12 cases. (There were 3 cases of complete external ophthalmoplegia, and in these the pupil was fixed to light.)

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The tendency for elevation of the eyes to be first affected in orbital disease has apparently been the experience of others. Cairns (1938) notes that the superior rectus is usually the first extraocular movement to be impaired in orbital abscess, tumour and in exophthalmic ophthalmoplegia. The rather selective vulnerability of this muscle was also pointed out in the ophthalmoplegia of Graves' disease by Rundle and Wilson (1944). In the present series the 2 cases of unilateral exophthalmos in which impaired movements of the eye existed without discoverable neoplasm, showed maximum weakness on upward gaze.

On review of the situation of the lesions causing extraocular muscle palsy, it became apparent that most instances occurred in intraorbital lesions (7 of 17 cases) and lesions involving the orbit with intraorbital extension (5 of 11 cases).

Of the intraorbital lesions producing palsies, three lay superiorly and presumably acted by direct pressure upon the superior rectus muscle (one sarcoma, one neurinoma, one mixed tumour of lacrimal gland). In two of these the lateral rectus was also involved and the lesion extended to an appropriate lateral position. Of the remaining 14 cases, 4 (1 meningioma, 2 lymphomas, 1 sarcoma) lay posteriorly in the orbit where opportunity was present for interference with both muscle and nerve function. That the former may predominate, however, was pointed out by the fact that only in the case of the meningioma was there interference with pupillary function. The remaining cases were sufficiently widespread to preclude an estimation of their point of maximal interference.

The other 12 instances of extraocular muscle weakness were scattered among the 49 cases of tumour involving the orbital or retro-orbital areas in various combinations. 4 of these were in association with an intracavernous aneurysm of the internal carotid artery with a fistula.

On the basis of the infrequent appearance of coincident internal and external oculomotor weakness with orbital tumour, it would appear that the mode of production of extraocular muscle weakness lies not so much in compression of major nerve trunks as in interference with the function of either the terminal motor twigs or the muscles themselves. If the degree of exophthalmos may be taken as a rough measurement of the degree of intraorbital pressure, it would appear that the pressure itself is not of critical importance. (The degree of exophthalmos in the group showing extraocular muscle weakness and the group without weakness was roughly the same.) The significant point in production of muscle weakness appeared to rest on whether this pressure was exerted as a local force within the orbit or as a general rise in intraorbital pressure. Thus there were but 12 cases of extraocular muscle weakness in forty-nine lesions involving orbit and retro-orbital parts (four due specifically to aneurysms), while twelve instances of palsy occurred in 28 cases with origin or spread within the orbital fascia.

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The reason is not clear for the rather selective and maximal involvement of the superior rectus muscle, with lesions in a variety of sites and including those cases of exophthalmos in which no tumour was found. Both the superior rectus and the levator of the upper lid are innervated by the superior division of the third nerve which divides just prior to passing within the annulus of Zinn. However, as mentioned above, the selective weakness of the superior rectus, with or without other palsies of the external ocular muscles, appears more frequently alone than with the concomitant palsy of the levator. Thus it would appear that the weakness is not due to a selective pressure block of their common innervation.

The answer may rest in the relative weakness of the superior rectus in man. One may convince oneself of this feature by attempting to keep the eyes elevated for any period. Rundle and Wilson (1944) have sought to explain this weakness on the fact that the superior rectus makes an angle of about 25 degrees with the sagittal plane of the globe. Therefore, when the eye is elevated from a point of central fixation the muscle is not working in its plane of maximal action. Also, the fact that the scleral insertion of this muscle is the farthest from the cornea of all the rectus muscles (Wolff, 1951, p. 209) may add to this mechanical disadvantage. It would be of considerable interest to learn whether a subclinical weakness of the remaining muscles might exist, at this time, in view of deciding whether the superior rectus is specifically involved or simply the first muscle to demonstrate, clinically, a minor but general weakness of all the extraocular muscles.

Summary

A series of 86 cases of unilateral exophthalmos seen and treated on a neurosurgical service were reviewed for consideration of the pathological and clinical characteristics of lesions producing this symptom.

On the pathological side, the invasiveness of meningiomas becomes evident once they pass into mesenchymal tissues, although their rate of growth is slow. Partial removal of gliomas of the optic nerve and chiasm may be attended by remarkably prolonged periods without recurrence or increase of symptoms. The frequency of fibrous dysplasia in the present series was unexpected and suggests that the lesion may at times go unrecognized. The term cholesteatoma proved confusing in the present material and it appeared that the lesions could be reclassified with advantage under more specific terms. Of 8 cases presenting unilateral exophthalmos without tumour, 2 were tentatively considered as examples of thyrotropic exophthalmos while 6 were associated with hypertension and 2 of these with glaucoma. Further cases are required to establish whether this indeed forms a syndrome and what part, if any, these features play in the pathogenesis of exophthalmos.

On the clinical side, macular, peripheral and intermediate defects in the visual fields were found and no good evidence was disclosed to explain the

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variations. Venous obstruction in the posterior orbit appears to be an important factor in the production of exophthalmos and the inadequacy of the anterior venous drainage from the orbit is noted. Papillœdema was seen with lesions posteriorly in the orbit, but not anteriorly, and seemed satisfactorily explained on a venous congestive basis. The relatively greater sensitivity of the parasympathetic fibres to pressure as compared with the motor nerve fibres has been demonstrated and indirect evidence suggests that sympathetic overaction has little to do with the mydriasis in orbital lesions. Review of the extraocular muscle palsies suggests that direct pressure upon the muscle is a more frequent cause of inactivation than is compression of its nerve supply in the orbit. The almost selective vulnerability of the superior rectus muscle to pressure was a frequent finding.

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PLATE X

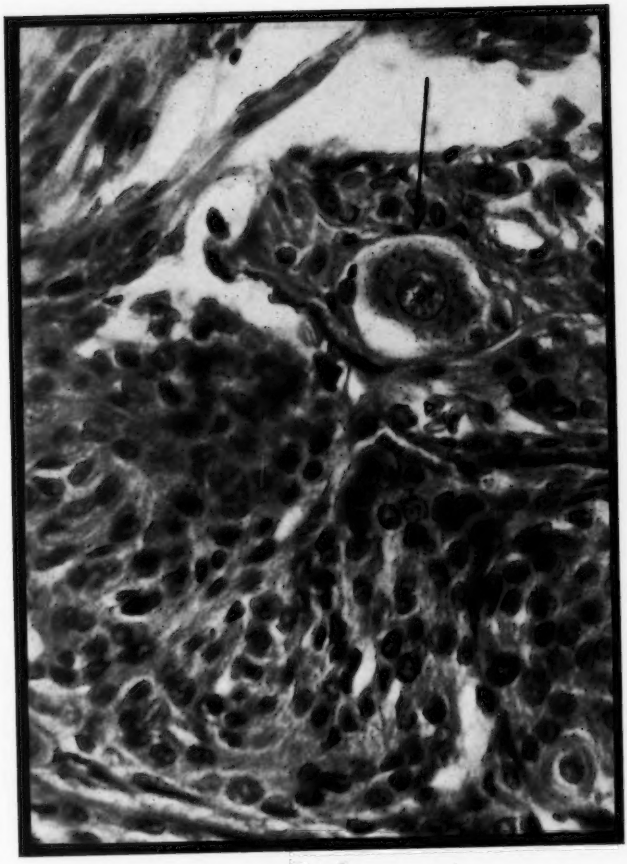

FIG. 1.

To illustrate article by J. M. Van Buren, J. L. Poppen and G. Horrax.

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PLATE XI

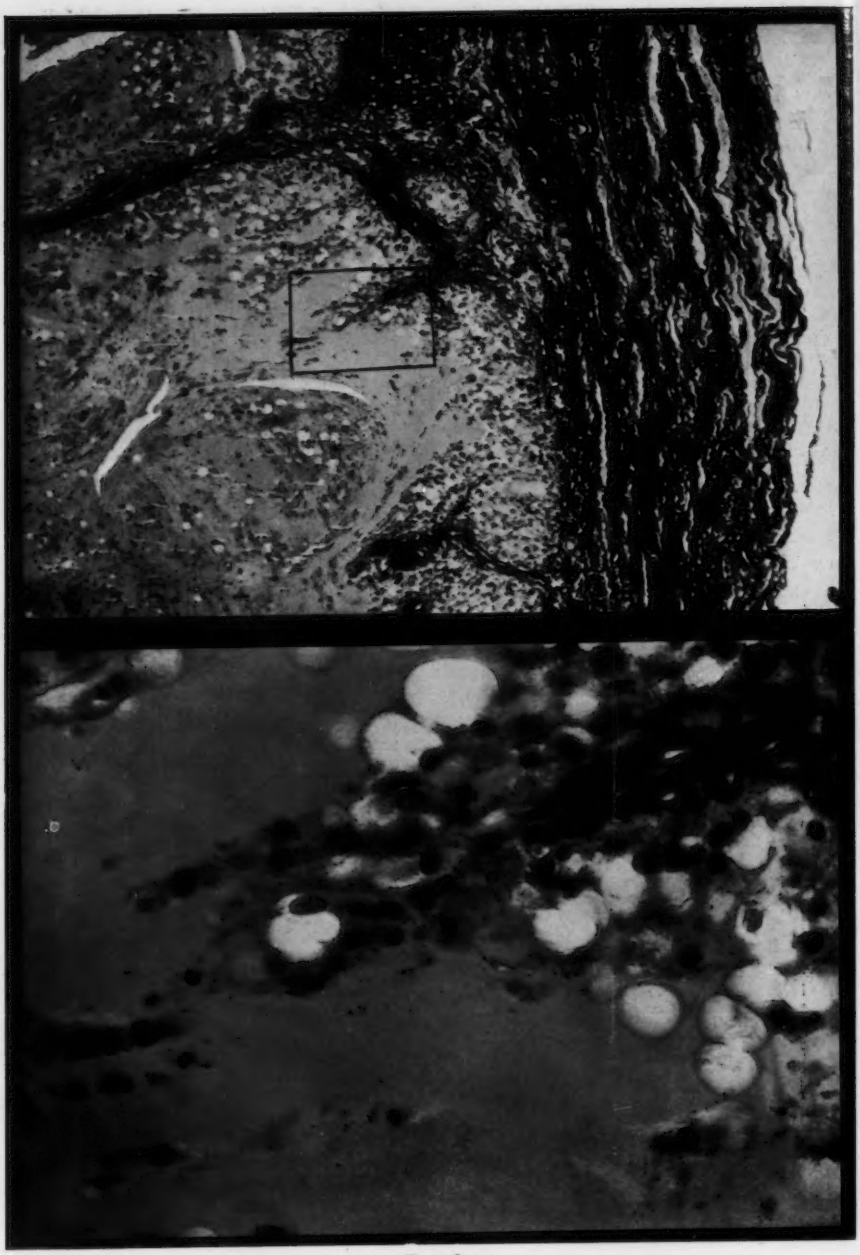

FIG. 2.

To illustrate article by J. M. Van Buren, J. L. Poppen and G. Horrax.

PLATE XII

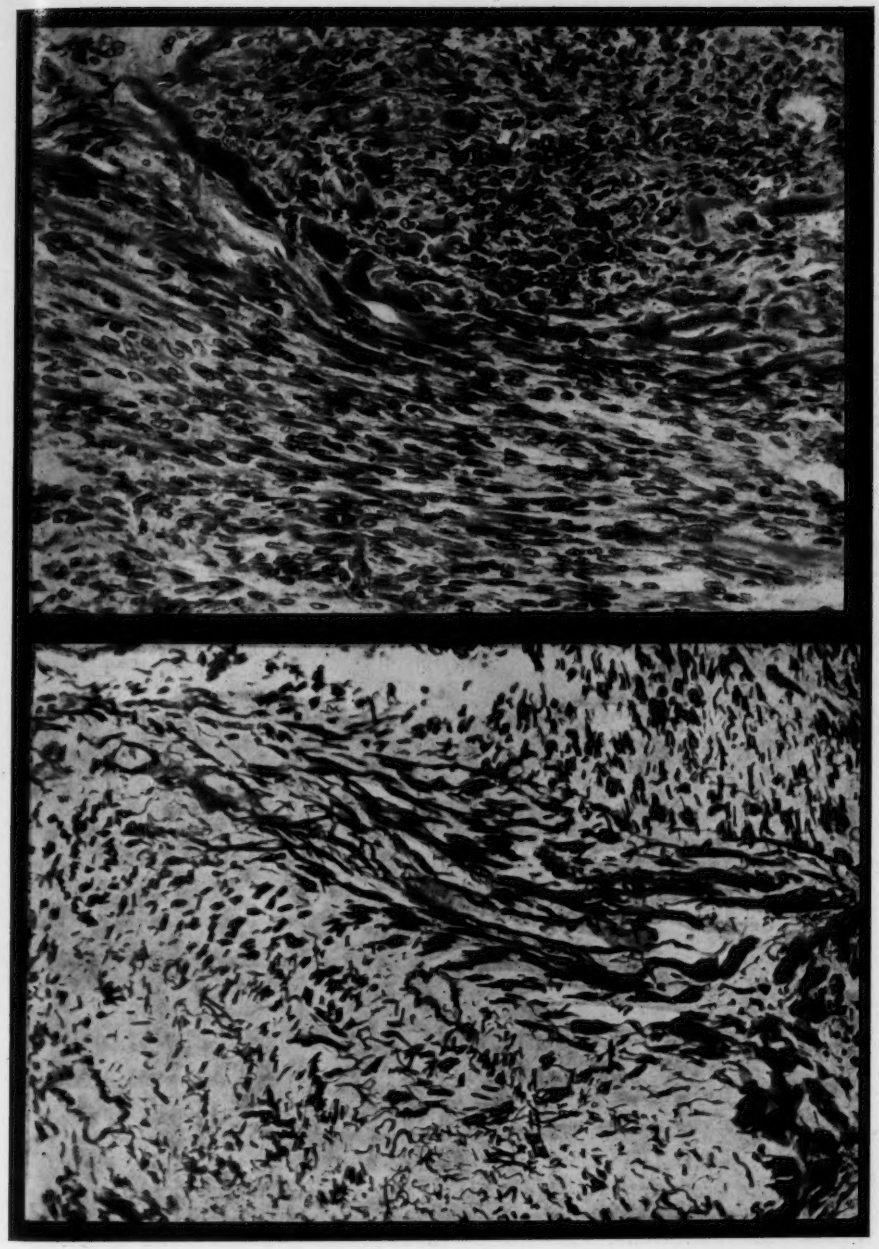

FIG. 3.

To illustrate article by J. M. Van Buren, J. L. Poppen and G. Horrax.

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PLATE XIII

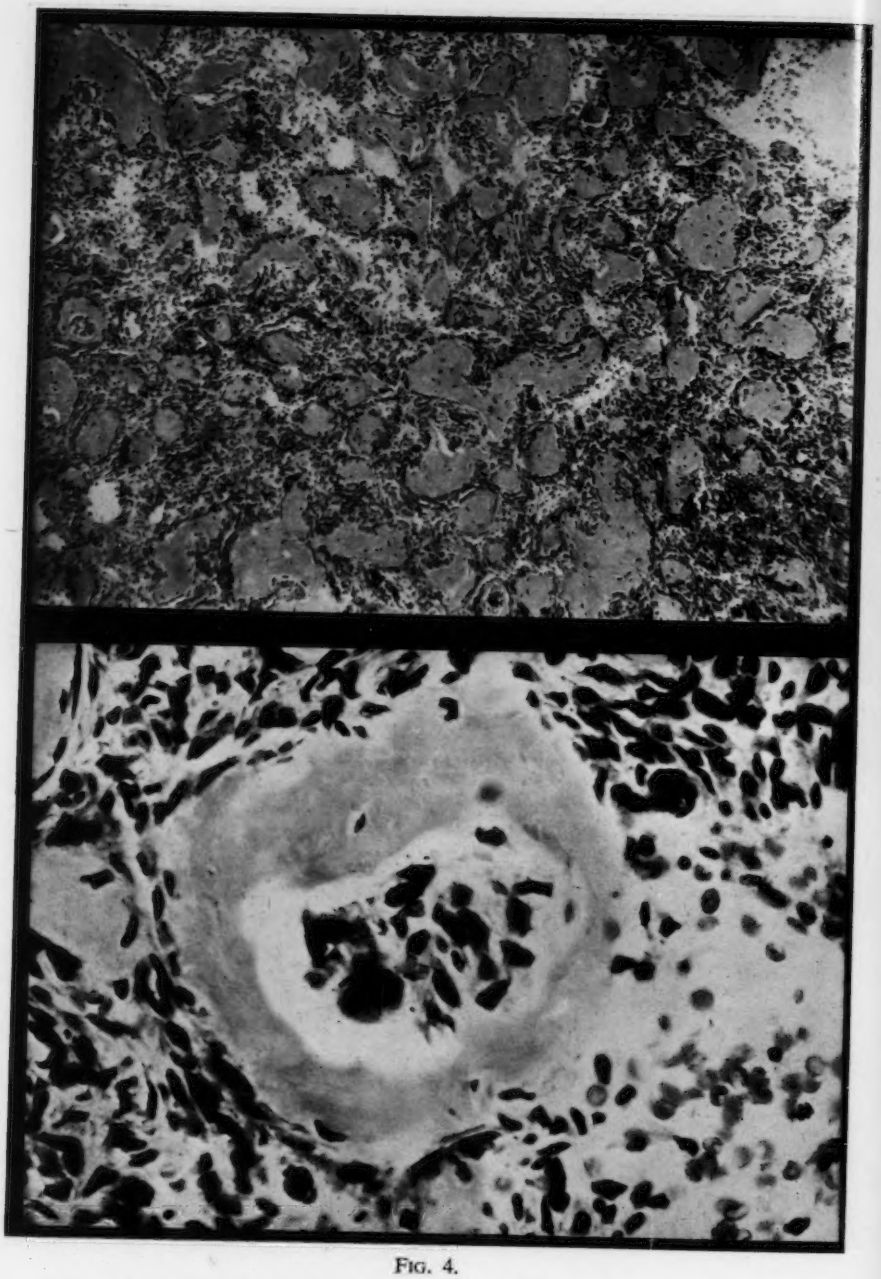

FIG. 4.

To illustrate article by J. M. Van Buren, J. L. Poppen and G. Horrax.

PLATE XIV

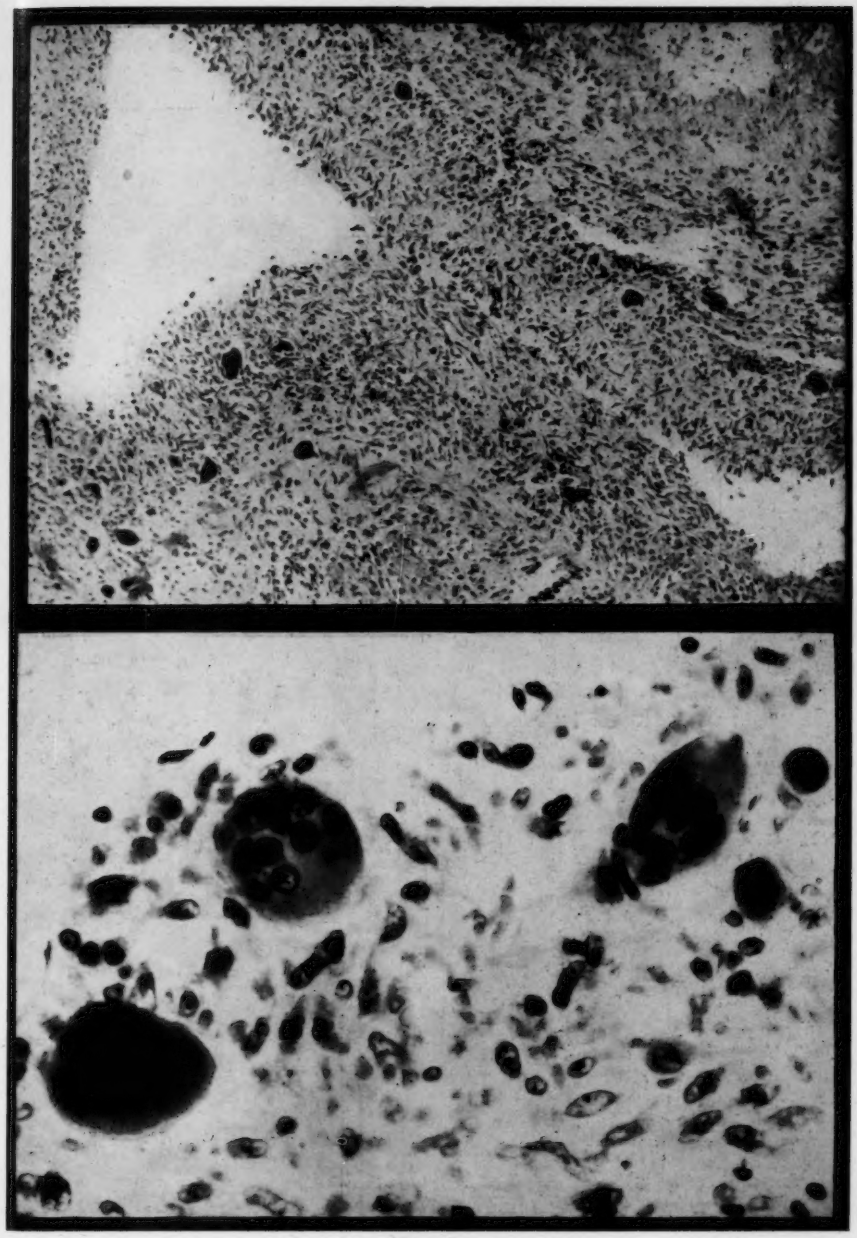

FIG. 5.

To illustrate article by J. M. Van Buren, J. L. Poppen and G. Horrax.

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FIG. 6.

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FIG. 8.

To illustrate article by J. M. Van Buren, J. L. Poppen and G. Horrax.

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LEGENDS TO PLATES

PLATE X

FIG. 1 (*Case 60*).—Meningioma invading the gasserian ganglion. The arrow indicates a ganglion cell engulfed by tumour cells. Hæmatoxylin-eosin, × 750.

PLATE XI

FIG. 2 (*Case 59*).—A glioma of the optic nerve showing marked myxomatous degeneration. The thickened pia-arachnoid should be noted. Phosphotungstic acid-hæmatoxylin. × 150 (above), × 750 (below).

PLATE XII

FIG. 3 (*Case 15*).—Neurinoma arising within the orbit with a massive intracranial spread. Above, phosphotungstic acid-hæmatoxylin; below Laidlaw's connective tissue stain, × 400.

PLATE XIII

FIG. 4 (*Case 33*).—Fibrous dysplasia. Osteoid island and ring formation. Hæmatoxylin-eosin, × 150 (above), × 750 (below).

PLATE XIV

FIG. 5 (*Case 58*).—Fibrous dysplasia. Fibroblastic overgrowth and giant cell formation. Masson's trichrome. × 150 (above), × 750 (below).

PLATE XV

FIG. 6 (*Case 53*).—Illustrates the striking perineural spread of a malignant cylindroma extending into the posterior portion of the orbit from the middle fossa. The primary tumour originated within the sphenoid sinus. Hæmatoxylin-eosin, × 150.

PLATE XVI

FIG. 8.—Stereoscopic views of the arteriogram done in Case 56. The large vessel indicated by arrows in the superior medial portion of the orbit proved on biopsy to be a vein.

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CHANGES IN THE NERVOUS SYSTEM IN ACUTE PORPHYRIA[1]

BY

RAYMOND HIERONS

*Neurological Department, King's College Hospital**

SIXTY-FIVE years have elapsed since there first appeared reports of neurological disturbances in this disease. In spite of the growth of a vast literature on the clinical and chemical aspects there have been few pathological reports. These are concerned chiefly with single cases and in most of them, little change was found in the nervous system. Moreover there is still little knowledge of the essential mechanism of the lesions that have been found.

It seems appropriate therefore to record 5 cases in which the pathological findings are in some respects unusual.

The earliest recorded case examined pathologically was by Campbell (1898) in which the central nervous system failed to show any significant abnormality. A little later Erbslöh (1903) and Abderhalden (1919) observed loss of myelin in the peripheral nerves. There followed descriptions of similar changes by Bostroem (1920), Snapper (1922), Harbitz (1924), Mason, Courville and Ziskind (1933) and others. Some cases failed to show any abnormalities in the peripheral nerves in spite of signs of polyneuritis during life.

Changes in the dorsal root ganglia were mentioned by Bostroem and later by Courcoux, Lhermitte and Boulanger-Pillet (1929). These changes consisted of chromatolysis of the ganglion cells, vacuolation of cytoplasm and occasionally of the nuclei. Denny-Brown and Sciarra (1945), Marchand and Ajuriaguerra (1949) have contributed excellent descriptions of these lesions.

Changes in the anterior horn cells of the spinal cord were seen in a number of cases. Courcoux *et al.* noted the presence of chromatolysis and a reduction in the number of these cells. Similar findings were recorded by Mason *et al.*, Abbott and Evans (1946), Marchand and Ajuriaguerra, Lapresle (1950), Grogg (1951), and Schwarz and Moulton (1954). The general opinion was that all these changes were secondary to axonal damage, although Marchand and Ajuriaguerra doubted this explanation.

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*Present address The Department of Neurology, The Brook Hospital, London, S.E.18.

Less severe changes in the ganglion cells of the dorsal horns have also been described. Slight demyelination of the marginal areas of the antero-lateral parts of the cord in one case was seen by Courcoux *et al.*

Lesions in the bulbar motor nuclei similar to those in the anterior horn cells were recorded by Mason *et al.* Other changes in the brain-stem consisting of vacuolar changes in the cytoplasm of the olives, small perivascular hæmorrhages, collections of plasma cells around vessels and subependymal gliosis of the floor of the fourth ventricle were noted by van den Bergh *et al.* (1937), Baker and Watson (1945) and Schwarz and Moulton. In the Purkinje cells Mason *et al.*, Abbott and Evans, Marchand and Ajuriaguerra, Hart and Collard (1950) observed chromatolysis of varying degrees. Minor changes also occurred in the dentate nucleus in which Schwarz and Moulton observed ischæmic and homogenizing cell changes.

Lesions in the cerebrum have been minimal or absent in the cases so far recorded although the majority of the patients experienced severe mental disturbances in life. Intense chromatolysis was noted in some of the giant pyramidal cells by Courcoux *et al.* together with fibrinous thrombosis of a vessel of the motor cortex. Another instance of slight uniform chromatolysis was given by Mason *et al.* who also noted the presence of occasional vacuolation of the cytoplasm and of the nuclei. In this young patient the neurones contained greatly increased amounts of fat. Other descriptions, Golden (1943) and Grogg, were of a patchy loss of ganglion cells with gliosis in these areas. Denny-Brown and Sciarra found only isolated darkly-stained neurones in the cortex. An interesting report was given by Schwarz and Moulton, in which they described extensive changes consisting of large numbers of ghost cells in the cortex together with chromatolysis, sclerosis and homogenizing cell changes. In this case there were also similar changes in the claustrum, putamen and globus pallidus.

Marchand and Ajuriaguerra, Schwarz and Moulton describe infiltration of the cerebral arterioles with lymphocytes and plasma cells. Phagocytic cells containing yellow or orange pigment were also seen in the walls of the blood vessels, particularly in the white matter and to a lesser degree in the cortex.

Small areas of perivascular demyelination without involvement of the axons were observed by Baker and Watson, Denny-Brown and Sciarra, Abbott and Evans and by Schwarz and Moulton.

Changes have been seen in the cells of the cœliac ganglion. They consisted of distortion of nuclei by intra- and pericellular vacuoles with an increase in lipoid. At the same time changes in the myelin and the presence of fat-staining phagocytes were recorded by Mason *et al.*

Case 1.—K. B., male, aged 14, was the fourth child in a family of 8. His eldest sister had died in 1952 from an acute illness diagnosed as Landry's paralysis. This began with abdominal pain, vomiting and convulsions followed by the development

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of hypertension and paralysis of all four limbs. Autopsy provided no abnormal findings but no histological examination of the nervous system was carried out.

Early in 1952 this boy, then aged 13, began to have short attacks of abdominal pain every few months. In July 1953 a more severe attack occurred with vomiting and a few days later several generalized convulsions occurred and as a result he was admitted to hospital. On examination a few small hæmorrhages were found in the left retina, the right knee-jerk was brisker than the left and the blood pressure was 170/110. Further convulsions occurred and the abdominal pain continued. Ten days after the onset he complained of stiffness of the legs. At this stage no weakness was detected and the reflexes were all present, but a few days later signs of muscle wasting and weakness with feeble reflexes appeared. At this stage bilateral papillœdema was present and the blood pressure 200/140. The urine was reddish-brown and darkened after exposure to light.

He was transferred to the National Hospital under Dr. Elkington on August 21.

He looked ill and cachectic, was drowsy although correctly orientated and co-operative when roused. A patchy amnesia was present for the previous few weeks. Slight neck stiffness was detected and straight leg raising limited to 60 degrees on both sides. Marked papillœdema was present on the left and the nasal edge of the right disc was blurred. Moderate generalized wasting of all four limbs was present together with marked muscle tenderness. Power was severely impaired, most distally in the upper limbs and proximally in the lower. He was unable to sit up without help. The knee-jerks and right triceps reflex were absent, other tendon-jerks were obtained with difficulty. The plantar responses were both weakly extensor. The urine contained a large quantity of porphobilinogen, also a trace of albumen and an occasional white cell.

The cerebrospinal fluid was under normal pressure and except for a protein content of 65 mg. per cent and a weak positive Nonne Apelt and Pandy it showed no other abnormalities.

Tests of liver function were within normal limits except for an alkaline phosphatase of 25 units. Blood urea was 30 mg. per cent. The pyruvate metabolism test was very abnormal:

Fasting blood pyruvic acid	= 0·88	mg. per cent
1½ hours after glucose	= 2·2	,, ,, ,,

This was repeated five days later when

Fasting level	= 1·0	mg. per cent
1 hour after glucose	= 1·68	,, ,, ,,
1½ hours after glucose	= 2·08	,, ,, ,,

The electro-encephalogram revealed a generalized abnormality most marked in the left temporo-parieto-occipital region.

Progress.—A series of generalized convulsions occurred six days after admission and he was afterwards restless and noisy for several days. Head retraction and marked neck stiffness were present together with a positive Kernig's sign. On account of this a further lumbar puncture was carried out. This revealed a pressure of 80 mm.; the fluid contained 7 white cells per c.ml. (4 lymphocytes, 3 polymorphonuclears) and 30 mg. of protein. He improved for several days but became once more confused and restless and occasionally dyspnœic without signs of congestive heart failure being noted. Further convulsions occurred and he was comatose during the last two days before death on September 4. The blood pressure during the last two weeks of life varied between 180–220 systolic and 145–180 diastolic. The lowest pulse-rate recorded was of 115 per minute and the rate was frequently 140.

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Pathological findings.—(Autopsy performed by Dr. W. Mair.) The lungs showed evidence of bronchopneumonia. About 10 c.c. of straw-coloured fluid was present in the pericardial sac, otherwise naked-eye and microscopical examination of the organs revealed no significant abnormality.

The brain and spinal cord presented a normal appearance. Material for histological examination was taken after fixation from all representative areas and stained by the usual methods.

In the cerebral cortex there were widespread pathological changes and they fell into two categories. Firstly, diffuse lesions—slight to moderate in severity and consisting of loss of nerve cells with neuroglial reaction. Secondly, severe focal lesions of different size and shape and clearly ischæmic in nature. The diffuse lesions were present in all the areas examined and probably affected all cortical regions. The loss of nerve cells was greatest in the second and third cortical layers, and the junction between the molecular and outer granular layers was frequently irregular and eroded. In the areas of greatest cell loss, some residual cells were seen to be stained darker than normal and showed a slight degree of granular incrustation while others appeared as faint cell remnants. The majority of neurones presented only slight alterations difficult to evaluate and the architectonics of the cortex were nowhere significantly disturbed. Associated with this cell loss there were varying degrees of neuroglial and microglial proliferation. The neuroglial proliferation was always marked in the molecular layer, where the cells were sometimes multinucleate with large cell bodies staining well in the Nissl preparations. The microglial reaction in the molecular layer was never so marked as the neuroglial reaction. In the cellular layers the neuroglial reaction was widespread although less severe in the deeper cortical layers where the loss of neurones was less definite. In Ammon's horn the neuroglial proliferation was marked in the end folium and associated with some loss of neurones. Changes in the rest of the pyramidal layer including the Sommer's sector were minimal.

The changes in the striate and parastriate area were not marked, but it was chiefly in the occipital cortex that the gross focal lesions were found.

In the most severe type of focal lesion all the cortical layers were involved (fig. 1). The external granular layer contained pale-staining nerve cells with vacuolar cytoplasm, others were shrunken with small pyknotic nuclei. In the third layer few nerve cells remained and these were either faintly or very darkly stained. In the deeper layers more of the large pyramidal cells were preserved. In such lesions considerable neuroglial proliferation, especially in the molecular layer, was present together with numerous microglial cells, some of these rod shaped with swollen elongated nuclei. In other layers neuroglial proliferation had also occurred and in the deeper regions many swollen microglia cells filled with fat were apparent. In the white matter underlying such lesions much neuroglial proliferation was present. In addition proliferation of endothelial cells and branching of capillaries was prominent throughout the depth of the cortex. Also present were occasional small hæmorrhages. Several lesions of this type were relatively circumscribed, affecting the greater part of one convolution with margins which either were sharp or faded more gradually into the adjacent cortex.

A somewhat different lesion was also observed in the occipital cortex consisting of areas stretching a few mm. with gross loss of neurones and disturbance of architectonics. In these areas great neuroglial proliferation, with some cells containing three nuclei, was seen. This was most pronounced in layers III and IV but occurred to a lesser extent throughout the cortex. This degree of cortical damage was not associated with any significant endothelial or fibroblastic reaction.

The neurones in the regions of better-preserved cortex surrounding these lesions frequently showed gross pathological changes, and many faint-staining residual fragments of nerve cells were present.

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The cortex also showed less severe focal lesions with small foci of cell loss, where many rod-shaped microglial cells filled the empty space.

In the left cerebral hemisphere a zone of hæmorrhagic infarction was present which involved the caudate nucleus, internal capsule and putamen. Slightly more posteriorly necrosis of tissue was present between the upper part of the claustrum and putamen. Still more posteriorly at the level of the geniculate body there was a small zone of hæmorrhagic infarction in the internal capsule, and neighbouring it a necrotic lesion in the upper part of the putamen. This necrotic zone contained thrombosed vessels with large numbers of compound granular corpuscles.

No significant abnormality was seen in the myelin of the rest of the cerebral hemispheres.

The vessels of the brain and spinal cord (except for the capillary proliferation in the areas of cortical damage) were normal. Brownish refractile pigment was present in the macrophages around the larger arteries of the white and grey matter but mainly in the white. This failed to stain with Prussian blue.

The cerebellum showed only slight changes. Many of the Purkinje cells were pale staining and it is probable that some slight loss had occurred; also the Bergmann glia cells were increased. In places the molecular layer was remarkably cellular and approximated to a scrub-like glial overgrowth with many microglial and endothelial cells present.

In the dentate nucleus many cells showed evidence of chromatolysis with lateral displacement of the nucleus. Some cells were darkly stained with an intact nucleus whilst in others the nucleus had almost disappeared (probably chronic cell changes).

There were no significant changes in the pons except for a small area of diffuse hæmorrhage with infiltration by microglial cells and destruction of a few pontine cells.

In the medulla a few cells of the hypoglossal nuclei were shrunken and darkly stained and a small proportion of those of the nucleus ambiguus showed signs of chromatolysis. The glia were increased in these nuclei, also in the olive, and the nuclei gracilis and cuneatus.

The meninges were thickened in places and occasional areas infiltrated with lymphocytes, plasma cells and a few polymorphonuclear cells.

In the spinal cord, a number of the anterior horn cells showed chromatolysis clearly indicative of axonal damage (fig. 2). A few neurones showed very marked vacuolation of the cytoplasm and occasionally in this type of cell there was fairly good preservation of the Nissl substance. It seemed probable that a few cells had disappeared and were replaced by small collections of astrocytes and microglia. Occasional shrunken cells were also present. These changes were most severe in the cervical region. The lumbar region, however, was without significant abnormality. The white matter of the spinal cord at these levels was normal.

No adequate material for study was available from the peripheral nerves.

In the posterior root ganglia slight capsular proliferation was present and a few ganglion cells showed evidence of chromatolysis, and less frequently vacuolation of the cytoplasm (fig. 3). Slight proliferation of the Schwann cells was also present.

In the sympathetic ganglia many neurones showed marked chromatolysis and others vacuolation. About 1 per cent of the cells contained two nuclei. Swelling of myelin especially at the nodes of Ranvier were observed, but no cellular infiltration was present.

Case 2.—I. C., female, aged 22, was admitted to hospital on October 25, 1949, on account of epigastric pain of about five weeks' duration together with occasional vomiting. For the previous year she had been losing weight and also complained of severe constipation and insomnia. Except that she was extremely depressed and had lost weight, examination did not reveal any significant abnormalities. There were

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no abnormalities of motor function or reflexes, and the blood pressure was 120/86. Routine urine examination, blood count and examination of the cerebrospinal fluid failed to reveal anything abnormal. A barium enema showed the colon to be of normal outline, but it is of interest that on re-screening ten days later, and in spite of several colonic washouts, distension with barium was still very obvious.

From the records it appears that she received large quantities of barbiturates, and in the course of narco-analysis by a psychiatrist became cyanosed, pulseless and almost died. She was transferred on November 7 to a mental hospital on account of her noisy behaviour.

Several days after her admission to that hospital she first noticed weakness of the legs which gradually increased and involved the trunk and spinal muscles. Except for feeble biceps and ankle jerks the other reflexes were absent; plantar responses were flexor. During this time she was often noisy and occasionally deluded, as a result barbiturates were frequently administered. In the last few weeks of life respiratory difficulties necessitated the use of a mechanical respirator. She died on January 31, 1950.

Examination of the urine on several occasions revealed the presence of porphyrins and porphobilinogen.

Pathological findings.—Autopsy was carried out by Dr. G. F. M. Hall twenty hours after death. The body was extremely wasted and a patchy brown pigmentation was present over the abdomen. Except for purulent bronchitis and a moderate degree of hypostatic pneumonia there were no other abnormalities, and histological examination, other than of the nervous system did not disclose further abnormal findings. Investigation of the various organs with ultraviolet light revealed the fluorescent appearance of porphyrins in the costal cartilages and in the urine and to a lesser degree in the kidneys, bile and the inner surface of the dura. Fluorescence was absent from other organs examined including the uncut brain.

The brain and spinal cord appeared normal to naked eye examination.

Histological examination revealed slight generalized thinning in all areas of the cerebral cortex examined. Some loss of neurones had occurred in all the cortical layers, associated with astrocytic and microglial infiltration. Gliosis was especially prominent throughout the molecular layer. Many small areas of loss of nerve cells were also present, chiefly in the third layer, and in these there was an increase of astrocytic and occasionally of microglial cells. In addition, in the parietal and occipital cortex there were several areas, each stretching for a few millimetres, with almost complete loss of cells from all layers, except that islands of pyramidal cells remained. Ammon's horn was, however, free from abnormality.

It was difficult to decide whether changes in the residual neurones of the cortex had occurred. Many cells had a triangular-shaped nucleus often with a crenated nucleolus.

Areas of demyelination, probably of recent origin were present in the cerebral white matter. In addition vascular proliferation, and an increase of astrocytes, especially just below the cortex, had occurred and œdema around vessels could be seen. The thalamus, globus pallidus and putamen were normal.

In the pons and medulla many neurones of the hypoglossal and nucleus ambiguus showed chromatolysis and in the latter there were glial nodules. The cerebellum, including the dentate nucleus, was normal.

Slight irregular thickening in the meninges was evident, but the blood vessels were everywhere free from abnormality.

In the spinal cord there were marked changes in the anterior horns. These consisted of loss of neurones with astrocytic proliferation and many of the nerve cells remaining showed chromatolysis clearly due to axonal damage. Several were shrunken or showed

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vacuolation of cytoplasm and in these the Nissl substance often had a normal appearance. These changes were present throughout the spinal cord but were most evident in the lumbar region. There was no sign of demyelination in the cord. The spinal meninges were slightly thickened and the nerve roots in several places showed swelling and irregularity of myelin.

In the peripheral nerves considerable loss of myelin and fragmentation was seen in osmic acid preparations of the sciatic (fig. 4), phrenic, median and ulnar nerves. Silver pyridine stains (fig. 5) showed clearly that the small myelinated and unmyelinated fibres were well preserved whilst only few large fibres remained. In addition, areas of macrophages, lymphocytes and occasional polymorphonuclear cells were present.

Case 3.—M. D. P., female, aged 31, was admitted to hospital in February 1951. She complained of lassitude, backache, abdominal pain and constipation of several weeks' duration, also insomnia which had led to the use of sedatives. On the day before admission, several generalized convulsions had occurred. The notes describe her as "anxious and hysterical"; except for signs of recent loss of weight nothing abnormal was found on examination. Increasing weakness of the limbs developed during the next ten days. The arms were severely affected, particularly at the shoulder girdles, and moderately severe generalized weakness was present in the lower limbs. The trunk muscles were also involved, and there was reduced movement of the lower ribs. The tendon reflexes, although sluggish, were all present and the plantar responses were flexor. No defect to any form of sensation was found, and general examination was completely negative except for a blood pressure of 160/90.

At this time the patient was transferred to another hospital and again her behaviour was considered to be hysterical. Her memory, however, for the previous two weeks was impaired. Physical examination did not reveal any further abnormalities. A diagnosis of acute porphyria was considered and was confirmed by the presence of large quantities of porphobilinogen in the urine.

During the next few months severe abdominal pain, intractable constipation, and pains in the limbs were constantly present. Generalized muscular wasting developed, and the tendon reflexes were all abolished. The pulse-rate was invariably raised to 140/minute. She complained occasionally of burning paræsthesiæ in the hands and feet but examination failed to reveal impairment of sensation.

Her condition improved a little during the next few months and she was transferred to a third hospital in June. Two weeks later she had several generalized convulsions and during the next few months was frequently confused, and occasionally deluded. Her speech became a feeble whisper but was considered by a throat specialist to be hysterical. Looking back on this period, it seems probable that further barbiturates were administered during the first week in this hospital. By October 1951 her mental state had completely recovered, although the limbs remained totally paralysed. Gradually some power returned, and eighteen months later she could feed herself and walk a few yards. As a result she was able to go home in June 1952. It appears that this improvement continued although exact information is lacking. The patient was able to continue at home until December 1953, when she was again admitted to hospital on account of increasing weakness of the limbs and confusion of two weeks' duration. For a few days her voice had been weak and there was difficulty in swallowing. She was found to be acutely ill, cyanosed and breathless. Signs of bronchopneumonia and paralysis of the diaphragm were observed, and she died the following day (there is unfortunately no record of the blood pressure during the last few years of life).

Pathological findings.—The autopsy twenty-four hours after death disclosed only purulent bronchitis and basal bronchopneumonia. The brain had been cut horizontally before being received, and appeared normal to naked-eye examination.

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In every area of the cerebral cortex examined, slight generalized loss of cells had occurred, together with increase of astrocytes especially in the third layer. Marginal gliosis was everywhere prominent, chiefly of astrocytes with occasional microglia. In addition, several small areas of cellular loss were present in all cortical areas. In these an increase of glia, including the gemistocytic form, some microglia and also new blood vessels were found (fig. 6). Beneath the pia several small areas of hæmorrhage were seen but in the absence of cellular response these were probably agonal or postmortem in origin.

Ammon's horn was relatively normal except for the end folium where astrocytic proliferation and some microglia were present.

In the thalamus small foci were present in which some neurones had a retracted outline, with dense nuclear staining and occasional infiltration of astrocytes.

There was no evidence of demyelination although astrocytic increase was present in the white matter of several gyri. In places the meninges were thickened and general vasodilatation was thought to be present. The cerebral vessels were otherwise completely normal. Brownish pigment, similar to that in Case 1 although much less marked was present in the macrophages around the larger arteries of the grey and white matter.

In the pons and medulla marked chromatolysis had occurred in the dorsal nucleus of the vagus, nucleus ambiguus and to a lesser degree in the hypoglossal, trigeminal and oculomotor nuclei, and proliferation of astrocytes was present in these areas. Swelling and irregularity of myelin was observed in the fibres of the oculomotor nerves, but otherwise the myelin was everywhere normal.

In several folia of the cerebellum there was some loss of Purkinje cells. In addition a few of these cells were enlarged and irregular in shape with loss of the nucleus and faintly stained cytoplasm. Other Purkinje cells were irregular and darkly staining. The Bergmann glia was slightly increased and there was possibly an increase in the glia of the molecular layer in scattered areas.

The spinal cord was not preserved and it was impossible to draw definite conclusions from the small pieces of peripheral nerves available for study.

Case 4.—W. D., male, a 21-year-old soldier, was admitted to a Military Hospital in the Middle East in July, 1951. He had complained for the previous year of severe constipation and frequent attacks of abdominal pain. In the week before his admission he experienced pain in the back and legs. Some days after admission he first noticed difficulty in standing, and power was then found to be considerably reduced in the quadriceps; the knee-jerks were also absent. Blood pressure was 170/110. Occasionally he was confused and difficult to manage. Examination of the urine disclosed the presence of porphobilinogen. During the journey by air to this country he was restless, confused and occasionally even violent so that several injections of barbiturates were given.

On admission to King's College Hospital under the care of Dr. Nevin he was emaciated (with a loss of 2 st. in weight) disorientated and confused. There were no abnormalities of special senses or cranial nerve functions. Severe muscular wasting and weakness were present in all four limbs. There was complete paralysis of the shoulder girdles and marked weakness of the trunk muscles. Slight cardiac enlargement was detected, blood pressure 190/120 and the pulse-rate was never less than 120 per minute.

Gradually his mental state and paralysis improved, and two months after admission he was able to walk a distance of a hundred yards. His weight increased and the pulse-rate fell to normal. In December he became depressed, and complained of insomnia. During the course of the next few weeks a recurrence of pain and weakness of the limbs occurred, and he was again confused. Reflexes (except for the ankle-jerks) were absent. He died in January 1952, after twenty-four hours in coma.

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The urine on a number of occasions revealed the presence of porphobilinogen. The electroencephalogram soon after admission was abnormal with a great excess of diffuse slow activity at 3–6 cycles per second and occasionally at 1–2/second.

Pathological findings.—The autopsy was performed by Dr. D. G. Rushton seventy-two hours after death (due to difficulty in obtaining permission).

Severe emaciation and muscular wasting were present. No naked-eye abnormality was found in the abdomen except that the entire large intestine was packed with scybala. The sternal marrow was the only tissue examined which was fluorescent. Microscopical examination revealed early bronchopneumonia. The brain and spinal cord appeared normal to naked-eye examination.

In the cortex loss of neurones seemed to have occurred in places surrounding areas of venous dilatation. Many of the nerve cells remaining appeared swollen with darkly staining nuclei and pale cytoplasm. Others were elongated and shrunken with darkly stained triangular-shaped nuclei. A slight glial increase had occurred, particularly in the molecular layer. These changes were present in all parts of the cortex and were most prominent in the post-central area, although the Betz cells were unaffected.

The meninges were thickened in places and contained brownish refractile pigment, and collections of cells chiefly lymphocytes.

In the basal ganglia the slight changes similar to those in the cortex were present. There was no sign of demyelination of the cerebral white matter.

The cerebellum (except for the dentate nucleus) was normal. In the latter some cells had disappeared and others consisted of a small cell body with a darkly staining nucleus. The pons and medulla were normal.

The blood vessels except for generalized vasodilatation were everywhere normal.

In the lumbar and cervical regions of the cord some loss of anterior horn cells had occurred. At the cervical level this was most evident in the lateral cell column. Many of the anterior horn cells showed central chromatolysis—clearly secondary to axonal damage. Several neurones had a vacuolated appearance of the cytoplasm—others were shrunken and a few small cells in the cervical region showed granular incrustations of their cell body without visible nucleus. Some increase in glia was present in these areas. In the lumbar region some of the posterior horn cells were pale staining. In the lower thoracic region except for atrophy of a few anterior horn cells and a small clump of glia in the posterior horn no significant abnormalities were seen. Only in the cervical region were the meninges slightly thickened. In the posterior root ganglia several cells were vacuolated and there was a slight proliferation of capsular cells.

In the peripheral nerves, osmic acid preparations revealed areas of swelling and fragmentation of myelin in different stages of degeneration. This was most marked in the ulnar and phrenic nerves and was of a moderate degree in the sciatic nerve, whilst in the median only a few lesions were seen. In these lesions zones of degeneration and macrophage infiltration were present.

Case 5.—N. I., male, aged 39. At 9 years of age he had an attack of severe abdominal pain and retention of urine. As a result the appendix was removed but was found to be normal. The pain continued and severe weakness of the legs developed during the post-operative period. During the next few months the paralysis completely disappeared, though the pain recurred at frequent intervals during the next few years and then completely ceased. At the age of 28 and after five years of Army Service, he developed a severe bullous rash over the arms after exposure to the sun but this cleared up within a few weeks. Subsequent exposure to the sun, however, was without effect.

He remained in good health until the age of 33 when an attack of severe abdominal pain associated with distension, constipation and vomiting occurred. A laparotomy

was performed without anything abnormal being found. These symptoms continued, weakness of the legs developed and he complained of paræsthesiæ in the buttocks and groins. Double vision was present for several days at this time. The muscular weakness gradually increased and the arms became involved. He was depressed, unable to sleep and was often delirious. His symptoms were thought to be hysterical and after returning home the weakness increased and he complained of constant abdominal pain.

He was readmitted on December 1, 1949. Examination revealed no significant abnormalities of intellectual functions or of the cranial nerves. In the motor system moderate weakness was present in the upper and lower limbs. Tendon reflexes, except for the ankle-jerks, were absent; both plantar responses were extensor. Pronounced muscle tenderness was present. No significant sensory loss was found. The C.S.F. was under normal pressure, contained 130 mg. of protein but without excess of globulin, Lange curve 0012210000 and with a negative serological reaction in the fluid as was the blood. The urine contained porphobilinogen and he was transferred to King's College Hospital on December 15, 1949.

On admission he was mildly depressed and during the next few weeks variable mental retardation was present with periods of emotional instability. He was able to repeat the Babcock sentence at the second attempt but made 3 errors in the serial seven test. No abnormalities of special senses or cranial nerve functions were detected. In the limbs moderate wasting and muscle tenderness were present. There was very severe weakness most marked distally in the upper and proximally in the lower limbs. The diaphragm was paralysed, and weakness of the lower abdominal muscles was present. In the upper limbs only feeble biceps-jerks could be elicited, the knee-jerks were present, the ankle-jerks were brisk, both plantar responses were extensor and the abdominal reflexes were absent. Impairment to pain and light touch was present over the lower abdomen and front of the thighs. Elsewhere no defect to any form of sensation was found.

General examination was negative except for a constant tachycardia of 100–150/minute, blood pressure was 135/85.

His mood varied in the first month from depression to marked euphoria, and he was occasionally confused and incontinent.

The electro-encephalogram was abnormal on several occasions with a slow alpha rhythm of 7 c/sec. and bursts of 2 c/sec. activity involving all cortical areas. These abnormalities were most marked in the left post-central area. Throughout January and February these changes continued although to a slightly lesser degree. By the end of March the alpha rhythm was about 8 c/sec. and the record had become almost normal.

The electro-cardiogram showed evidence of a right bundle branch block, and this remained unchanged on several occasions.

X-ray of the chest was normal.

The urine contained porphobilinogen. The quantity gradually dwindled and by March 1950 had disappeared. About this time also he began to improve rapidly: the incontinence disappeared, and his mental state became normal. His limbs became free from pain, and power improved. By May the only appreciable weakness involved the extensors of the fingers and wrists. Tendon reflexes were now feeble in the upper limbs; the knee and ankle jerks were very brisk with ankle clonus on the right and bilateral extensor plantar responses.

After returning home in May he continued to improve although the pyramidal signs persisted. In November another attack of abdominal pain occurred associated with constipation and vomiting. After readmission to hospital he was mildly confused for several days, and he had retention of urine. There was no change, however, in the neurological signs, and the attack subsided within two weeks.

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During the next few years he was liable to almost constant aching pain in the abdomen and occasional bouts of severe colic. As a result he became addicted to pethidine, taking large quantities daily by injection. He complained also of aching pain in the lower end of the tibiæ, which often kept him awake at night. Other symptoms included depression, poor concentration, irritability and tension. He was able to walk about two miles before his legs started to drag, and was subject to occasional flexor spasms of the legs at night. On account of the pethidine addiction he was admitted again to hospital in November 1954.

Psychological testing (Dr. H. Himmelweit) revealed no evidence of intellectual deterioration. The patient's family, however, reported that his intellect and memory were not as good as before the episode in 1949. The abnormal signs consisted of some increase in tone in the lower limbs, and minimal weakness of the hip flexors. All reflexes were pathologically brisk including the jaw-jerk, the abdominal reflexes were diminished and the plantar responses both extensor. No defect to any form of sensation was detected.

Further investigation included a barium meal which showed no radiological abnormality.

The EEG revealed an excess of slow activity mainly at 3–6 c/sec. in the post-central regions.

The addiction to pethidine was gradually overcome, and his abdominal pain appeared to be fairly well controlled by codeine phosphate and he remained well after his return home. In June 1955 a recurrence of abdominal pain occurred with frequent vomiting. About a week later he suddenly coughed up large quantities of frothy blood-stained sputum, and died within half an hour.

Pathological findings.—The post-mortem was carried out by Dr. D. G. Rushton twenty-eight hours after death. Marked autolytic changes had taken place (death had occurred at home at the height of a hot summer). The findings included marked congestion of the lungs and the presence of blood-stained fluid in the bronchi. The myocardium was pale and flabby, and slight narrowing of the coronary arteries due to atheroma was observed without signs of fresh thrombi. Moderate atheromatous changes were present in the aorta. The liver was pale with signs of chronic congestion and several stones of " mixed type " were found in the gall-bladder. The kidneys had a finely granular surface and there was slight thinning of the cortex. Histologically the only abnormality was patchy glomerular destruction and fibrosis of the kidneys obscured by severe autolysis.

The brain and spinal cord appeared normal to naked-eye examination.

The cerebral cortex, except for marked hyperæmia was everywhere without significant abnormality. Ammon's horn and the basal ganglia appeared normal. The white matter of the cerebral hemispheres was excessively cellular in places and around the vessels the appearances suggested the presence of œdema. There was no indication of demyelination in the cerebral hemispheres.

In places the meninges were more cellular than normal and these areas were infiltrated with lymphocytes.

In the cerebellum there were a number of small areas in which the Purkinje cells were absent or considerably reduced in number. Some of these cells were shrunken or pale-staining, and in places in the molecular layer astrocytic and microglial proliferation had occurred.

The pons and medulla appeared normal including the myelin at these levels.

In the spinal cord about 50 per cent of the anterior horn cells had disappeared and some of the remainder appeared shrunken. Astrocytic proliferation and a few microglia were present in the anterior horns. These changes were most marked at the cervical level but were present to a lesser degree in the dorsal and lumbar regions. Some posterior horn cells showed signs of chromatolysis. Demyelination was evident

in the cord at all levels examined (fig. 7). The posterior columns were uniformly involved in the lumbar region whilst in the dorsal and cervical region the changes were confined to the medial part of the dorsal funiculus with a normal appearance of the lateral part. Pallor of lesser degree was present in the lateral columns—most marked in the lumbar area and very slight in the dorsal and cervical regions. A longitudinal section of the posterior column of the dorsal region (Glees's stain) showed many well-preserved axons (fig. 8).

The posterior roots were slightly pale, chiefly in the lumbar region but no very marked changes were visible. No definite abnormalities were seen in the sciatic and femoral nerves. It was not possible to draw conclusions as to the presence of changes in the sympathetic ganglia due to the presence of autolytic changes.

Case 6.—Mrs. R. N., aged 42 (sister of Case 5), was admitted to a mental hospital after an abdominal operation, hallucinated, deluded and frequently confused. At the same time weakness of the limbs had developed, which was considered to be hysterical. She was transferred to King's College Hospital in January 1955 when she had signs of severe polyneuritis with sensory loss.

Investigations included an abnormal pyruvate tolerance:

Fasting level						= 1·15 mg. per cent			
30 minutes after 50 grammes glucose						= 1·0	,,	,,	,,
60	,,	,,	,,	,,	,,	= 1·35	,,	,,	,,
110	,,	,,	,,	,,	,,	= 1·55	,,	,,	,,

Biopsy, the sural nerve.—In the osmic preparation disappearance of myelin was apparent in places. In other fibres it was grossly distended and fragmented into sausage shapes and globules of varying size (fig. 9). Unfortunately the remaining piece of nerve which it was intended to study in other preparations was lost.

Biopsy of muscle at the same time showed proliferation of the sarcolemma without evidence of interstitial inflammation. The appearances were suggestive of commencing neural atrophy.

Discussion

Abnormalities were present in all these cases in the anterior horn cells, when the spinal cord was available for study. The changes were present to a variable degree at every level examined—except that the lumbar region of the first case showed no significant abnormality. The chromatolysis was clearly secondary to axonal damage, and does not require further consideration. In the literature, other changes in the anterior horn cells are frequently discussed along with chromatolysis. It seems extremely unlikely, however, that axonal damage can explain the vacuolation of the cytoplasm in some of these neurones and also the presence of shrunken cells. In addition, in Case 4, granular incrustations were observed in a few cells. A further reason for assuming that vacuolated cells could not be likened to chromatolysis, was that the Nissl substance was frequently well preserved in these cells. Only in Case 5 were vacuolated cells absent, and in this patient the last acute episode occurred four and a half years before death. Some loss of cells also occurred in every case. This was greatest in Case 5, with the longest survival, in which about half of the anterior horn cells had disappeared. It is therefore possible that vacuolation may be a stage in cell loss.

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If these changes result from a primary effect of the disease on the anterior horn cells, this may be a metabolic process—either as a direct toxic effect on the cells or by means of a homologue-blocking enzyme. An alternative explanation is that vascular spasm causes minute focal lesions. It seems more likely on the whole that the changes are primarily metabolic, although the occasional granular incrustations in one instance make it difficult to exclude the possibility of a direct vascular factor.

Demyelination of the spinal cord was present in only one case (5). The posterior and lateral columns were affected, particularly in the lumbar region, and to a lesser degree in the dorsal and cervical areas. Although during life extensor plantar responses were present, several careful examinations in the four years before death failed to detect the slightest impairment of postural sense or other sensory deficit. The finding of well-preserved axons in the demyelinated posterior columns suggests that the pathological process responsible is one damaging primarily myelin.

In 3 cases material from the peripheral nerves was available. The changes present consisted of considerable loss, fragmentation and swelling of myelin often with macrophage infiltration. In 1 case only good axon preparations were available. This showed a loss of the majority of large fibres with preservation of the small and also the unmyelinated fibres. The idea of a vascular basis for the lesions in the disease, both central and peripheral, was originally put forward by Denny-Brown and Sciarra and this was based to a large extent on the peripheral nerve lesions. They described small gaps in the myelin at the nodes of Ranvier of the nerve roots, and to a slight degree in the peripheral nerves, whilst the axis-cylinders were intact throughout. These changes, they considered, were similar to those resulting from experimental ischæmia. In the cases described here the lesions in the peripheral nerves appear to be very different from those resulting from pressure ischaemia. Denny-Brown and Sciarra also claimed that absence of sensory change was the rule in porphyria and again analogous to ischæmic paralysis. Sensory impairment was present in 2 of these cases and this is occasionally marked, as for instance in Case 6. Here we were able to obtain a biopsy from a purely sensory nerve. It would also seem that the symmetry of the polyneuritis and the good recovery that can occur after virtually complete paralysis is unlikely to be the result of vascular lesions in the nerves. Some disturbance of biochemical function therefore appears more likely to explain these features. This explanation is perhaps supported by the finding of abnormal pyruvate metabolism in 2 of these cases. This abnormality was also present in another case not included here. Unfortunately nothing is known as to the nature of these metabolic effects—either in the nerves or spinal cord. The essential mechanisms, however, are equally obscure in the peripheral and spinal cord degenerations occurring in other metabolic conditions. The demyelination of the posterior and lateral columns in

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Case 5 is a finding of some interest as it has not been previously described in the disease. In the case of Courcoux, Lhermitte and Boulanger-Pillet the demyelination in the cord was extremely slight and affected only the marginal areas of the antero-lateral parts of the cord. This finding is almost certainly not of vascular origin.

To consider the cerebral changes, the findings in these cases clearly establish the occurrence of gross vascular lesions in the disease. In the first case these were severe and extensive in the cortex, and as the blood vessels were entirely normal in this boy of 14, a functional vascular disturbance must have occurred. As the blood pressure was extremely high—220/180 was recorded before death—it seems probable that vascular spasm secondary to the hypertension caused the lesions, a sequence which has been well demonstrated experimentally by Byrom (1954).

Moreover there is considerable evidence for the occurrence of vascular spasm in the disease. Attacks of transient blindness were reported by Waldenström (1937) and Denny-Brown and Sciarra observed narrow retinal vessels. Watson (1954) has also observed this in several cases: in one the arterial narrowing occurred repeatedly, and simultaneously with convulsions. Raynaud's phenomenon has appeared in some of these patients. Details are not always clear in published cases, but it is probable that hypertension is an important feature of patients with these disturbances.

The occurrence of abdominal pain and severe constipation as a constant feature of the condition also suggests some disturbance of smooth muscle function of the intestinal tract. Mason *et al.* have suggested that the abdominal symptoms result from lesions in the autonomic system. Changes similar to those described by these authors were found in my first patient. I recently encountered a patient in whom surgical exploration was undertaken for the abdominal pain, before the correct diagnosis was suspected. At laparotomy a number of small hæmorrhagic areas were found in the cæcum and terminal ileum. This would suggest that vascular lesions similar to those in the nervous system can occur.

It is now necessary to consider the cause of the mental disturbances which are such a prominent feature of the majority of patients. The question arises whether this can be attributed to gross vascular lesions. These were most pronounced in the first case and this was the only patient in whom the typical psychological manifestations were absent. On the other hand the characteristic mental state was present in the second patient but in this case generalized loss of neurones was present in all layers of the cortex, most prominent in the third layer. Respiratory paralysis had occurred in this patient, so that these histological changes might well have been due to anoxia. Areas of demyelination in the cerebral white matter were also present associated with vascular proliferation and œdema; these also could have resulted from anoxia. Other cases in the literature,

in whom demyelination of the deep white matter was observed, have died with respiratory paralysis. In Case 3, in whom mental disturbances had been present, several small areas of infarction similar to those of the first case were found. In this patient unfortunately no observations of the blood pressure were recorded during the acute attacks in the last three years of life. There was also slight generalized loss of neurones together with gliosis, in the third and molecular layers of the cortex. Mental changes also occurred in the fourth case but only slight loss of neurones was found in the cortex. However, many nerve-cells were swollen, with darkly stained triangular nuclei and pale cytoplasm. In the fifth patient mental symptoms had been present five years before death but there was no evidence of residual vascular lesions in the cerebral cortex.

It is therefore not possible to correlate the gross vascular lesions with the mental disturbances and this is strongly supported from a review of the literature. In the majority of cases previously reported, changes in the cerebrum have been absent or minimal.

One might consider the possibility that focal vascular spasm may occur in the nervous system, not of sufficient intensity to result in gross vascular lesions. The possibility that spasm may occur in the disease without hypertension is suggested by Berg's observations (1945). He reported a case where the number of capillaries in the nail-bed were decreased and occasional aneurysmal dilatation was present. In this patient, daily recordings of the blood pressure were usually normal, and never higher than 150/100. It has also been claimed that porphyrins cause contraction of the intestine and uterus when applied locally, but, due to difficulty in obtaining preparations free from histamine, these observations cannot yet be accepted.

Although vascular spasm might explain the slight cortical changes which were the sole findings in Cases 2 and 4, the absence of clear ischæmic changes in the neurones would make this suggestion a most improbable one.

It is, however, difficult to express a confident opinion as to whether any specific cortical lesions, other than on a vascular basis, exist in this disease. The generalized loss of cells which was found in 4 of these patients could possibly be specific, but it seems more likely that these changes can be attributed to anoxia from respiratory paralysis or to the effects of convulsions.

An alternative explanation for the psychological disturbances and one which seems more likely from the evidence available, is that they result from functional, reversible changes in the neurones. The mental disturbances are comparable to those produced by mescaline, lysergic acid and other drugs, histological changes not being apparent, at least in the present state of our knowledge. Further histological investigation with tissue fixed very soon after death, might throw further light on these questions.

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The changes described here in the dentate nucleus and Purkinje cells (present in Cases 1, 3, 4 and 5) were similar to those previously described, except that the ischæmic or homogenizing changes reported by Schwarz and Moulton were not observed. These changes were similar to the diffuse changes present in the cortex and may be due to anoxia or to the effects of convulsions.

Future studies might be directed to the detection of minor neuronal changes and their differentiation from the vascular lesions.

Summary and Conclusions

(1) The pathological changes in 5 cases of acute porphyria are described and discussed in relation to the clinical features of the disease.

(2) It is considered that the peripheral nerve lesions probably result from a metabolic disturbance and not from vascular spasm.

(3) In the anterior horn cells considerable neuronal changes occur, probably metabolic in origin, as well as central chromatolysis resulting from the peripheral nerve lesions.

(4) Extensive vascular lesions can occur in the brain, but these are probably secondary to severe hypertension or respiratory paralysis, and are not the cause of the severe mental disturbances.

(5) It is considered that the mental disturbances are probably due to a direct, possibly reversible, metabolic effect of the disease; and this may result in some affection and loss of neurones in the brain and cerebellum similar to that in the spinal cord.

I wish to thank Dr. S. Nevin who suggested this work and gave me constant encouragement and advice during its preparation. I am grateful to Professor A. Meyer, Dr. W. Blackwood, Dr. B. S. Cardell, Dr. J. B. Cavanagh and Dr. J. Gruner for their generous advice and to King's College Hospital, Research Fund, my appreciation of the grant for technical assistance. My thanks are also due to the physicians and pathologists already named for the clinical details and post-mortem material. I am indebted to Mr. G. Harwood for the photographs.

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LEGENDS TO PLATES

PLATE XVII

FIG. 1 (*Case* 1).—Nissl × 30, Occipital cortex showing a severe focal lesion with loss of cells involving all layers.

FIG. 2 (*Case* 1).—Nissl × 200, cervical cord showing chromatolysis, vacuolation and shrinkage of anterior horn neurones.

FIG. 3 (*Case* 1).—Nissl × 130, posterior root ganglion-cervical region to show chromatolysis and vacuolation of cells.

FIG. 4 (*Case* 2).—Osmic acid preparation × 180 sciatic nerve showing almost complete loss of myelin.

FIG. 5 (*Case* 2).—Silver pyridine × 200, sciatic nerve to show small myelinated and unmyelinated fibres are well preserved whilst only a few large fibres remain.

FIG. 6 (*Case* 3).—Van Gieson × 70 frontal cortex showing small area of infarction with capillary proliferation.

PLATE XVIII

FIG. 7 (*Case* 5).—Heidenhain × 8 showing demyelination of the column of Goll.

FIG. 8 (*Case* 5).—Glees × 200, longitudinal section of posterior column showing many axons.

FIG. 9 (*Case* 6).—Osmic acid preparation × 180. Biopsy of sural nerve showing loss, distension and fragmentation of myelin.

PLATE XVII

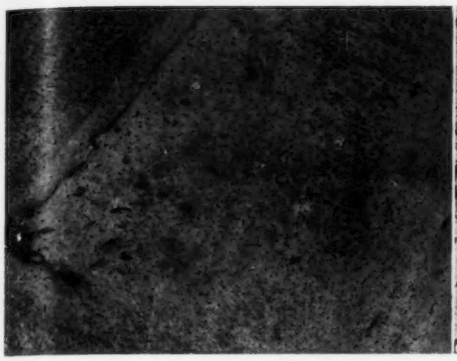

FIG. 1.

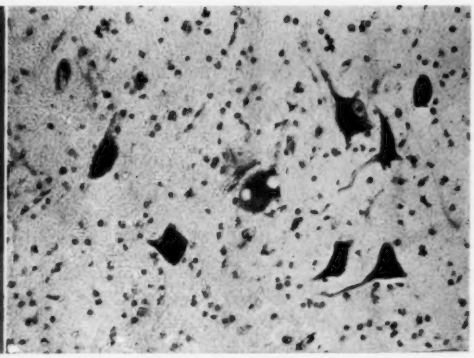

FIG. 2.

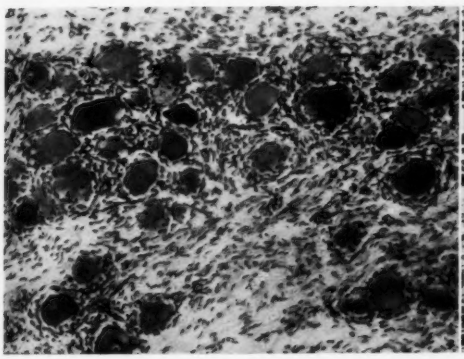

FIG. 3.

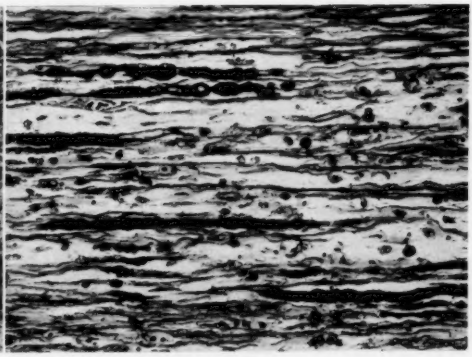

FIG. 4.

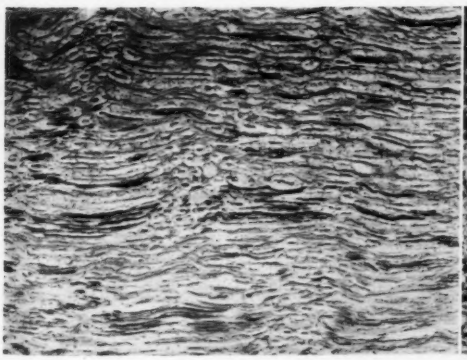

FIG. 5.

FIG. 6.

To illustrate article by Raymond Hierons.

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PLATE XVIII

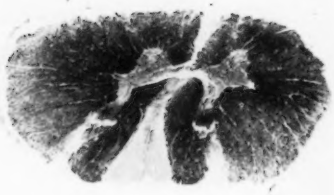

FIG. 7.

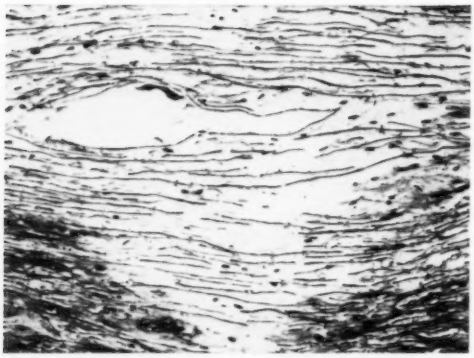

FIG. 8.

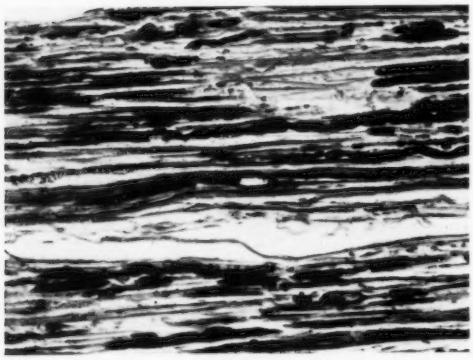

FIG. 9.

To illustrate article by Raymond Hierons.

THE INCIDENCE OF AMMON'S HORN SCLEROSIS

BY

J. A. N. CORSELLIS

Runwell Hospital, Wickford, Essex

ONE of the more controversial issues in the pathology of epilepsy is the incidence and the interpretation of Ammon's horn sclerosis. Although this abnormality is known to occur in the brains of many epileptic patients its incidence in the various series on record ranges from 5 to 80 per cent. Furthermore, when series of other conditions, such as the psychoses associated with senility and cerebral arteriosclerosis, general paralysis of the insane, or cases of mental deficiency are examined, lesions of the Ammon's horns are also found with remarkable frequency (Bratz, 1920; Crome, 1955; Morel and Wildi, 1956).

As a result of such evidence—that lesions of the Ammon's horns may occur as frequently outside the epileptic population as inside it—the conclusion tends to be drawn that no particular relationship exists between Ammon's horn sclerosis and epilepsy.

Such an inference, however, is not entirely satisfactory for there is considerable evidence from other sources (Penfield and Jasper, 1954) that the infero-medial parts of the temporal lobe are in fact of peculiar importance in certain kinds of epilepsy. Moreover, it is not easy to examine the post-mortem material of a mental hospital and yet to look on the association of epilepsy and changes in the Ammon's horns as either infrequent or irrelevant.

Finally, since the surgical removal of a temporal lobe to include the hippocampal formation has been widely used as a method of treatment in epilepsy, it is of some practical importance to try and throw any light on this problem.

The present investigation is therefore an attempt to do this by estimating the incidence in general of lesions of the Ammon's horn and their relation in particular both to the occurrence of convulsions, and to the diagnosis of epilepsy.

CASE MATERIAL

200 cases have been investigated. In 64 of these one or more convulsions were known to have occurred during life; in the remaining 136 none had been recorded.

With the exception of those cases in which epilepsy had figured as

part of the diagnosis all cases were first classified irrespective of the presence of convulsions.

The cases were accumulated from the routine post-mortem examinations carried out in mental hospitals but a small number (28) from general hospitals were also included in order to widen the range of the material. Cases were selected only in so far as this was necessary to build up an adequate number of each of the main categories.

Group 1.	Normal and neurotic persons; non-organic psychoses	65 cases
Group 2.	Mentally defective patients	14 ,,
Group 3.	Psychosis associated with cerebral arteriosclerosis ..	30 ,,
Group 4.	Senile psychosis and Alzheimer's disease	29 ,,
Group 5.	Other organic cerebral conditions	30 ,,
Group 6.	Epilepsy	32 ,,

In each case blocks were taken from the posterior half of the hippocampal formation of both sides. These were embedded in celloidin and sections, in the first instance, were stained with cresyl violet. Other staining methods (for myelin, Van Gieson's, Mallory's phosphotungstic acid hæmatoxylin and Holzer's methods) were used when required and in the great majority of cases sections were available from other areas as well. A normal Ammon's horn has been illustrated for reference (fig. 1) and the various fields mentioned in the text have been indicated. the term, field h1, has been taken as synonymous for the Sommer sector. All low-power illustrations are at the same magnification: × 11.

Pathological Findings

An abnormality in the Ammon's horn of one or both sides was found in 55 of the 200 cases and the distribution in the various groups was as follows:

Group 1. Normal and neurotic patients; non-organic psychoses:

Composition:

Normal or neurotic	19 cases
Schizophrenic/paranoid series	33 ,,
Affective psychoses..	13 ,,

The various types of schizophrenia, the paranoid states and the affective psychoses are considered here to have no known organic basis. The cases therefore are taken as equivalent to normal in so far as the present investigation is concerned.

Total of 65 cases, 39 female, 26 male. Average age at death 57, ranging from 18 to 92 with 31 cases over 60.

Death was attributed to the following conditions: Heart disease 22 cases; respiratory disease 15; malignant disease 14; other conditions 14.

In 5 of the 65 cases lesions were present in the Ammon's horns:

(1) 26/56. Female, catatonic schizophrenia. Very occasional convulsion, the first at the age of 20. Pre-frontal leucotomy aged 51. Died age 55 after several

convulsions. Post-mortem examination showed the right lung to be densely adherent to the chest wall with a marked scoliosis. Both lungs were œdematous and the right side of the heart was dilated with slight hypertrophy of the myocardium. Brain: leucotomy lesions in both frontal lobes. Superficial scarring of the cortex of the tip of the left temporal pole (1 cm. diameter) and anterior half of left olfactory tract. Rusty staining of the right temporal tip. In both Ammon's horns many of the nerve cells, especially in h1. showed "ischæmic change" (fig. 2). Similar neuronal changes also seen elsewhere in the cortex.

(2) 96/54. Female, paranoid schizophrenia. Died aged 75 from bacterial endocarditis. Brain slightly swollen, with acute purulent meningitis. Right Ammon's horn—h1 field swollen and necrotic. Marked loss of nerve cells with much proliferation of rod cells (fig. 3) and slight astrocytic proliferation. Inflammatory exudate in angle of ventricle with cuffing of vessels by leucocytes in the underlying white matter adjacent to h1. The left side showed similar but much slighter changes.

(3) 54/55. Female, asthmatic for many years, died aged 57. Admitted following convulsive attack and hæmatemesis. Death after twenty-four hours. Acute gastric erosions, periarteritis nodosa affecting vessels of stomach, liver, and adrenals. Brain: meningioma 2 cm. diameter on floor of right middle fossa indenting the cortex 2 cm. lateral to the medial border of the uncus. Cerebral vessels intact. The h1 field on both sides appeared swollen (fig. 4), the nerve cells shrunken or very pale, and many showed ischæmic changes.

(4) 39/52. Female, manic-depressive psychosis. Died aged 59, twenty-four hours after the last of a number of convulsive treatments (Inj. leptazol leading to *grand mal* attack). Post-mortem findings included marked atheroma of the aortic arch and coronary vessels and a very severe kyphoscoliosis with marked pulmonary emphysema and cor pulmonale. Right Ammon's horn—complete necrosis of h1 with many compound granular cells around the vessel walls.

(5) 2/56. Female, depression. Age 53, suicide by strangulation. Ischæmic nerve cell change marked in both Ammon's horns.

In addition to Case 1, 3 more had at some time suffered from convulsions—1 following a leucotomy and in 2 other schizophrenic patients occasional fits had occurred. In these 3 cases the Ammon's horns were normal.

In at least 10 cases one or other form of convulsive treatment had been given but the only case to show any lesion of the Ammon's horns was Case 4 above.

Group 2. Mentally defective:

Tuberose sclerosis	..	2 cases
Gargoylism ..	..	2 „
Mongolism ..	..	2 „
Other single cases	..	8 „

Total of 14 cases; 9 female, 5 male. Average age at death 27, ranging from 5 to 68. In 10 cases death was attributed to lobar or bronchopneumonia and in one to myocardial degeneration. Of the remaining 3 one death followed convulsions, one died from tuberculous peritonitis and one death was unexplained.

In 3 of the 14 cases lesions were present in the Ammon's horns:

(1) 28/53. Female idiot. Maternal toxæmia, premature birth, forceps used. Onset of convulsions aged 9, died aged 14 from bronchopneumonia. Brain: gross

atrophy and almost complete loss of cortex and white matter of the right hemisphere. The Ammon's horn on this side lay on the medial edge of the atrophic area and was distorted by it. Within the subiculum, and to a lesser extent the h1 field, there was a patchy loss of nerve cells and some gliosis. The left side was unaffected.

(2) 77/53. Male idiot. Cerebral diplegia, athetosis and epilepsy. Died aged 59 from myocardial degeneration. On both sides the Ammon's horns were completely sclerosed.

(3) 87/53. Feeble-minded male, pseudohypertrophic muscular dystrophy, severe kyphoscoliosis. No history of convulsions. Gradual mental and physical deterioration to death at 14 from bronchopneumonia. In both Ammon's horns the h1 fields were necrotic, most of the nerve cells had disappeared and there was an intense microglial proliferation. The remaining fields were unaffected.

In one case, therefore, without convulsions and in 2 with them the Ammon's horns were affected; in 4 further cases with convulsions no such abnormality was found.

Group 3. Psychosis associated with cerebral arteriosclerosis.

Total of 30 cases, 14 females, 16 males; average age at death 70, ranging from 49 to 93.

Gross cerebral lesions due to vascular disease were seen in 22 cases; cardiac hypertrophy had been noted in all but 2 cases. Death was attributed to malignant disease in 2 cases but vascular disease of the brain or cardiac disease accounted for the great majority of cases.

In 13 of the 30 cases lesions were present in the Ammon's horns. In 3 they were bilateral, in 5 on the right and in 5 on the left side.

Convulsions had occurred in 5 cases—in 2 of these lesions were present in the Ammon's horns (both were also hypertensive—*see below*), in 3 none was found.

In 11 of the 13 cases with Ammon's horn lesions a blood pressure of systolic 210 or over and/or diastolic 110 or over had at some time been recorded. Of the 17 cases without an Ammon's horn lesion a similar level had been present in 9.

Group 4. Senile psychosis (19 cases) and Alzheimer's Disease (10 cases).

Total of 29 cases, 20 female, 9 male. Average age at death 74, ranging from 54 to 92. In 13 cases death was attributed to myocardial degeneration and in 12 to bronchopneumonia; in the remaining 4—1 was due to carcinoma of the lung, 1 to staphylococcal meningitis and 2 to pulmonary infarction.

In 16 (5 being Alzheimer's Disease) of the 29 cases an abnormality of the Ammon's horns was found. In 12 this was bilateral, in 1 it was right-sided, in 3 on the left.

Convulsions had occurred in 3 cases of Alzheimer's disease, in each of which bilateral hippocampal lesions were present but these were also present in 2 cases without convulsions. In the earlier history of one

case of senile psychosis convulsions had occurred but in this case the Ammon's horns were normal.

Hypertension was present in 7 cases and in 3 of these the Ammon's horns were affected.

Group 5. Miscellaneous organic cerebral conditions.

Cerebral tumour	8 cases
Cerebral syphilis	4 „
Huntington's chorea	3 „
Pick's disease	2 „
Jakob-Creuzfeld Disease	2 „
Others	11 „

Total of 30 cases, 12 female and 18 male. Average age at death 56, ranging from 21 to 80. Death in most cases was attributable to the cerebral condition.

In 3 cases the Ammon's horns were abnormal:

(1) 65/55. Male, aged 21, died following convulsions. Brain—cerebellar ependymoma with spread to the medial surface of both temporal lobes. On both sides, but especially on the right (fig. 5) the tumour had invaded the medial edge of the hippocampus. On this side, h1 appeared swollen and pale and there was a considerable loss of nerve cells with much microglial proliferation, h3 to 5 were affected less severely. On the left a similar area of necrosis was present in the subiculum.

(2) 54/55. Male, aged 75. GPI. The right Ammon's horn showed a patchy loss of nerve cells and some gliosis in h1.

(3) 71/54. Male, aged 74. GPI with severe cerebral arteriosclerosis. Died of a cerebral hæmorrhage. Right Ammon's horn contained small infarcts scattered through the h1 field.

In 11 cases convulsions had occurred—5 with cerebral tumours, 2 in GPI, 1 in Huntington's chorea (in which there was also the scar of temporal lobe abscess) and in 3 cases of unclassified pre-senile dementia. In 2 of the 11 the Ammon's horns were affected—Cases 1 and 3 above.

Group 6. Epilepsy.

Cryptogenic epilepsy	27 cases
Symptomatic epilepsy	5 „

Total of 32 cases, 22 female, 10 male. Average age at death 57, ranging from 2 to 77. Death was attributed to the following causes: 9 died following convulsions or in status epilepticus, with evidence in 4 of heart failure and in 2 of pulmonary œdema. Bronchopneumonia was found in 7 cases and myocardial degeneration in 3, malignant disease in 3, hypertensive heart disease in 2, other causes in 8.

Fourteen of the cases of cryptogenic epilepsy came from mental hospitals and 9 from a home for non-defective, non-psychotic female epileptics (although such criteria were not strictly applied). 3 children and 1 adult came from general hospitals. The average age at death of the 27 patients with cryptogenic epilepsy was 46.

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To infants, who died in status epilepticus and one adult are summarized:

(1) 9/51. Female. First convulsion aged 2, severe attack at 3 of generalized convulsions. Marked cyanosis, followed by coma with intermittent twitching for two days. Finally Cheyne-Stokes respiration, periods of apnœa lasting half a minute. Brain: widespread laminar necrosis of cerebral cortex with marked astrocytic proliferation. Similar necrosis and gliosis in the right Ammon's horn, especially of h1.

(2) 49/56. Male. First convulsion at 1 year, twenty-four hours before acute infection, further attack aged 15 months at time of measles rash, again at 19 months with pyrexia of unknown origin. Final attack, aged 2, several convulsions followed by deepening coma. Periods of apnœa, death within twenty-four hours. Post-mortem examination: lung abscess, 3 cm. diameter. Brain appeared slightly swollen but no evidence of uncal or cerebellar herniation. Widespread ischæmic nerve cell change especially marked in right Ammon's horn but present in both (and elsewhere in cerebral cortex).

(3) 37/52. Male, convulsions since 1 year. Died age 39 from carcinoma of lung with mediastinal obstruction. Last convulsion three months before death. The left Ammon's horn was completely sclerosed; on the right, groups of nerve cells showed ischæmic change.

The 5 cases of symptomatic epilepsy were patients with cerebral lesions and an enduring history of convulsions associated with behaviour or personality disturbances (fits occurring on an average over a period of thirty-nine years). The average age at death in these cases was 66.

Lesions were present in the Ammon's horn of 15 out of the 32 cases—in 4 they were bilateral, in 3 right-sided and in 8 on the left. 14 of the 15 were cases of cryptogenic epilepsy.

Discussion of Findings

The incidence of the lesions of the Ammon's horns in the six groups can therefore be summarized as follows (fig. 6).

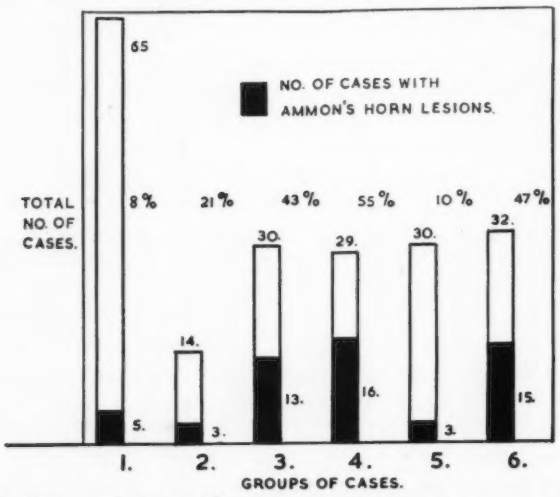

Fig. 6.—Incidence of lesions of the Ammon's horn in the six groups of cases.

Diagnostic group	*Total No.*	*Sex*	*Average age at death*	*No. with Ammon's horn lesions*	*R*	*Both sides*	*L*	*%*
1. Normal, neurotic; non-organic psychoses	65	m. 26 f. 39	57	5	1	4	0	8
2. Mentally defective	14	m. 5 f. 9	27	3	1	2	0	21
3. Arteriosclerotic psychosis	30	m. 16 f. 14	70	13	5	3	5	43
4. Senile psychosis Alz. disease	29	m. 9 f. 20	74	16	1	12	3	55
5. Miscl. organic cerebral disease	30	m. 18 f. 12	56	3	2	1	0	10
6. Epilepsy ..	32	m. 10 f. 22	57	15	3	4	8	47

If these cases are now considered as a whole, in 26 of the 55 cases with lesions of the Ammon's horn one or more convulsions had occurred during life, in 29 no convulsion had been recorded. Out of the 64 cases therefore in which convulsions had occurred 38 showed no structural change in either Ammon's horn. On the other hand, lesions were common in the presence both of arteriosclerosis (Group 3—an incidence of 43 per cent) and in cases of senile psychosis and Alzheimer's disease (Group 4—an incidence of 55 per cent). That is to say, in both these groups the incidence is of roughly the same order as that of the epileptic group of patients (Group 6—an incidence of 47 per cent, or if only the cryptogenic cases are taken—52 per cent).

Figures such as these compare reasonably closely with those of Morel and Wildi (1956) who found the following incidence in equivalent groups:

Cerebral vascular disease 47 per cent, senile dementia 45 per cent.

Alzheimer's disease 20 per cent, "Epilepsie dite essentielle" 18 per cent.

Although this last figure (based on 2 cases out of a total of 11) is appreciably lower than that in the present series the figures do in general appear to support the vie that the importance of damage to the Ammon's horn in epilepsy has been atly exaggerated in the sense that this structure is as frequently damaged ... patients without convulsions or conversely is as frequently spared in those with them—"in fact it certainly appears that no relation exists between Ammon's horn sclerosis and epilepsy."

There are two reasons, however, why such a conclusion may not be justified. Firstly, a diagnosis of epilepsy is not the same thing as the occurrence of one or more convulsions, and secondly, the term Ammon's horn sclerosis has been taken to include any pathological lesion of this area.

The problem is not necessarily the demonstration of a link between a convulsion and any lesion of the Ammon's horn. It may only confuse

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the issue to group together indiscriminately cases in which periodic convulsions have been the one outstanding—and yet inexplicable—feature for the greater part of life and those in which an occasional convulsion has appeared only in the course of a particular disease.

It may be important therefore to separate off this sub-group of cryptogenic epileptic cases from all other groups, including even those clinically most akin—the symptomatic epilepsies (as defined in Group 6)—in which, although convulsions may have been the predominant feature for many years a clearcut and presumably antecedent lesion of the brain was present.

With regard to the second objection, it seems clear that the term Ammon's horn sclerosis has been used to cover too wide a field, for there is good reason to believe that a number of different morphological entities have been subsumed under this one title. For example von Braunmühl in 1938 drew a clear distinction between the hippocampal changes in the epileptic and in the senile brain, while Scholz (1951) has pointed out that the commonest finding in the arteriosclerotic brain is the circumscribed infarct very different in appearance from the diffusely scarred Ammon's horn of the epileptic patient.

It may, of course, be argued that in this particular problem the appearances of the lesion are insignificant compared with the fact that they are there at all, but this cannot be assumed. It is equally possible that differences in the final histological picture may point to a more fundamental difference in its origin.

In order to get precise information on this point the 55 cases with lesions of the Ammon's horn were therefore examined in more detail. Firstly, the lesions were charted diagrammatically in each case and, secondly, a half-plate photograph of each affected horn was taken at a magnification of fifteen. In this way a more exact comparison, and one that could be easily verified, was made. The results are summarized below.

Different Lesions of the Ammon's Horn

Four different grades of lesion were identified, and on this basis the cases could be divided into four groups:

(*a*) The earliest change that can be identified is the "ischæmic nerve cell change" (fig. 2) and this was occasionally seen when death had followed shortly after convulsions or a period of hypoxia. With time to develop the changes become more established, the h1 field looks pale and swollen (figs. 4 and 5), many of the nerve cells disappear and an intense glial reaction takes place, predominantly of microglia in the form of rod cells (fig. 3). Astrocytic proliferation is also present and becomes predominant as the time lengthens. The Sommer sector is more severely affected than the areas h3 to 5 or the dentate gyrus; h2 is the least affected.

(*b*) A diffuse and virtually complete loss of nerve cells has occurred in h1 with a concomitant glial reaction, essentially astrocytic, the cells evenly but sparsely distributed throughout the affected area with the formation of a glial fibrosis. The fields h3 to 5 and the dentate gyrus are affected in a very similar way but usually to a slightly less severe degree; h2 is relatively spared. In this type of lesion the Ammon's horn is often shrunken and the appearances are, in short, those of old fibrous scarring—the classical Ammon's horn sclerosis (figs. 7 and 8).

(*c*) One or more circumscribed patches or streaks of nerve-cell loss with a concomitant glial reaction scattered anywhere in the Sommer sector, the relative intensity of the different changes depending to a large extent on their age. Less often other fields, including h2, or the dentate gyrus may be the seat of a similar small infarct (fig. 9). The streaked or patchy appearance contrasts with the more even distribution of the diffuse lesions. The neighbouring vessels often show degenerative changes and small cysts may be present.

(*d*) A diffuse lesion mainly affecting the Sommer sector in which a severe, but variable and by no means complete, loss of nerve cells is present. The affected area is not shrunken but it appears empty, pale and moth-eaten. The borders of the sector may be relatively well-defined by the large number of glial nuclei running along each side (fig. 10). Although the glial fibrosis may be dense beneath the ependyma and in the adjacent white matter, the Sommer sector itself is more cellular with a much finer formation of fibres. In silver impregnations many of the remaining nerve cells show neurofibrillary tangles and some senile plaques are present (fig. 11).

Relation of Type of Lesion to Original Diagnosis

If the cases are now put into these four categories and their original diagnosis is charted against them the following is found.

(*a*) *Acute lesions.*—Group 1: Cases 1 to 5. Group 2: Case 3. Group 5: Case 1. Group 6: Cases 1 to 3.

In these 10 cases acute lesions were present and it is usually possible to identify or at least to infer their precise cause (apart from the fact that in 6 of them convulsions had occurred not long before death). Of the 4 without such convulsions 1 died from meningitis, 1 died from asphyxia and 1 was a mental defective with muscular dystrophy, a terminal bronchopneumonia and a gross deformity of the chest and spine. It is suggested that the lesions in this case were related to the inevitable respiratory embarrassment and this is mentioned again later. The fourth case was that of an epileptic who suffered, three months after his last fit, an asphyxial death due to mediastinal obstruction by a carcinoma of the bronchus.

Of the 6 cases with convulsions before death, the lesions in 1 were

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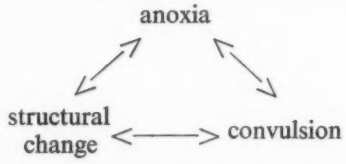
clearly related to the presence of a cerebral tumour, 2 were infants dying in status epilepticus in whom a severe degree of hypoxia must have occurred, and 1 was a long-standing asthmatic who in addition to her convulsive attack, suffered a series of gastric hæmorrhages. The remaining 2 resembled, to some extent, the mental defective just mentioned, for although no obvious explanation of the lesion was demonstrated, both suffered from severe deformities of the thoracic cage (in one the vertebral column was lying just medial to the head of the humerus) as well as a marked degree of lung and heart disease. Thus it seems justifiable to infer that in these cases a combination of factors was present which together proved overwhelming. Perhaps the similarity of the relatively unusual post-mortem findings would be an odd coincidence if this were not the case.

In general terms there seems adequate evidence therefore to interpret the changes according to the mechanism described so clearly by Lindenberg (1955) when he wrote "it can be shown that lesions in the hippocampal region may occur . . . in any type of supratentorial, increased intracranial pressure. Such may be caused by local space-taking lesions or by a generalized brain swelling in the course of a febrile or toxic illness . . . a mechanical head injury or an acute, systemic hypoxia which may develop even in epileptic attacks." In other words, the lesions may not be so much directly related to the presence of convulsions but rather the convulsions themselves may be the clinical manifestation of a pathological process common to both. Beyond this point it is impossible to go for the circle seems unbreakable—



since each can produce, or be produced by the other.

Nevertheless, the fact remains that acute lesions of the Ammon's horn may be found both as a sequel to anoxia and as an accompaniment of convulsions. Furthermore, if an acute lesion can be found in this way, presumably—if the patient survives long enough—the end-result will be a scar, that is a sclerosis.

(*b*) The second type of lesion comprises 15 cases showing the classical Ammon's horn sclerosis. Of the 19 horns which showed this change 16 belonged to the epileptic group of cases (Group 6), 2 to an epileptic mental defective (Group 2, Case 2), and one to one side of a case of senile dementia. It must be emphasized, however, that such figures are misleading to the extent that, as with acute lesions, such a sclerosis may also be found apart from epilepsy in patients who have survived

a past episode of severe cerebral hypoxia—whatever the cause (e.g. carbon monoxide poisoning, Hiller, 1924; hypoglycæmia, Lawrence, Meyer and Nevin, 1942). Such cases are not represented in the present material and are in fact probably very rare but to ignore their existence might lead to the presumption of too specific a connexion of epilepsy with Ammon's horn sclerosis.

(*c* and *d*). The third and fourth categories include all the cases of arteriosclerosis and of senile psychosis (with the exception of one side of the senile dementia mentioned under *b*) and also the two cases of GPI and one mental defective (Group 2, Case 1) in which the lesion was part of a cortical hemiatrophy.

With regard to the problem of general paresis (in which the incidence of Ammon's horn lesions is known to be high, Morel and Wildi, 1956) only 2 cases with such lesions were examined and 1 of these was complicated by severe arteriosclerosis. There is therefore no adequate material on which to make any comparative analysis of the lesions in this condition, although in neither of the 2 cases mentioned was a classical Ammon's horn sclerosis found.

The bulk of the cases therefore readily fall into the different groups with noticeable regularity and remarkably little overlap. Occasionally a case with arteriosclerosis may develop an acute lesion very similar in appearance, apart from the presence of degenerating vessels, to that found in group (*a*), but it would be remarkable if this were not the case. In the same way such a lesion might be expected to progress, if survival were long enough, to complete sclerosis.

In a number of cases both senile and arteriosclerotic changes were found together but since their precise separation is irrelevant to the present study this has not been attempted. The fact that the two conditions are to some extent intermingled is not surprising, however, since although many cases occur in which one or other process is predominant they are in no way mutually exclusive, for arteriosclerosis is not uncommon in the presence of senile changes (Bodechtel, 1930). The main difference seemed to be that the focal type of lesion of group *c* tended to occur unilaterally (this might not be the case if serial sections were examined) and was commoner in the presence of arteriosclerosis and hypertension while the more diffuse lesion of group *d* appeared to be a particularly intense part of the general disintegration of cerebral tissue that occurs in senile dementia and Alzheimer's disease—that is, the neurofibrillar changes and the loss or pigment atrophy of nerve cells, the formation of senile plaques and possibly the related vascular changes.

Lesions such as these, therefore, whether focal or more diffuse, were found almost exclusively in the presence of severe arteriosclerosis, or in the senile—both conditions in which widespread degenerative changes are taking place throughout the brain and in which the average age at death of those with lesions of the Ammon's horn is 74. It is therefore

only in the rarer, younger, severely hypertensive patients or in the cases of Alzheimer's disease that such lesions will presumably begin to develop much before the age of 65 is reached.

In the cryptogenic group of epileptic patients on the other hand no such connexion with advancing age seems apparent for in this group the average age at death of those with Ammon's horn sclerosis is 57. Moreover in direct contrast to the onset of disease in the senile and arteriosclerotic groups, convulsions do not start in the epileptic cases in the last years of life (unless death occurs when very young) but are usually present for the greater part of their existence—the average length of survival from the first fit in 24 of the present cases (all from Group 6 in which such information was available) was thirty-four years. If only cases with Ammon's horn lesions (acute or sclerotic) are taken, the survival is even longer—forty-three years.

It may be relevant, therefore, to compare the histological findings in these groups, for while in the arteriosclerotic and senile cases lesions of the Ammon's horns had clearly existed, even in the same brain, for variable lengths of time, in the cryptogenic epileptic group, with only three exceptions, there was always a well-developed scar. The three exceptions were the two infants in whom there had presumably been insufficient time for a scar to develop fully and the case in which death was largely due to asphyxia, unconnected with the patient's epilepsy.

Moreover, in those cases of cryptogenic epilepsy in which no sclerosis of an Ammon's horn was present careful search did not reveal any other lesion of more recent onset. (This is not meant to imply that changes do not occur in the epileptic brain subsequent to the initial disturbance. That they do is clearly shown in fig. 12 in which a fully sclerosed Ammon's horn is seen next to an area of hæmorrhage. Scholz (1951) moreover described lesions of various ages in the Ammon's horns of a case of "genuine Epilepsie" who died at the age of 31, but the case was exceptional in that 200 fits had occurred at one time within twenty-four hours!) Nevertheless, in those of the present cases in which convulsions had been occurring at intervals for many years and more or less up to the time of death no Ammon's horn showed evidence of having been recently affected. Even in the 8 cases in which death occurred after a bout of convulsions or in status epilepticus the only Ammon's horns to show evidence of this were those of the infants and those of a leucotomized schizophrenic patient (Group 1, Case 4) who might possibly be considered to fall into this group.

Such findings may at first appear to contradict the previous reports on epilepsy. For example, Scholz (1951) frequently described acute lesions in his cases, and it may be suggested that the present material is misleading. Another possibility, however, is that it is complementary, for the average age at death of all Scholz's cases was 14; in the present group

it was 57. The inference is clear—that the damage to the Ammon's horns tends to occur at least in the earlier years of life.

Until recently, however, there has been no satisfactory explanation of why Ammon's horn sclerosis occurs in some cases and not in others. It was generally accepted that the damage, in this peculiarly vulnerable area, occurred as a result of anoxia accompanying the epileptic attack. In 1953, however, Earle, Baldwin and Penfield suggested that while the cause of the damage might well be based on anoxia, the anoxic episode itself occurred during difficult birth, as a result of a localized compression of the blood supply, caused in its turn by the herniation of the temporal lobe. Meyer, Beck and Shepherd (1955) have qualified this conception on the grounds that certain patients with epilepsy who show Ammon's horn sclerosis start their clinical history—and the initial disturbance can be dated with reasonable certainty—several years after birth. Moreover, cases have been reported (Scholz, 1951; Group 6, Case 2 of present series) in which fresh lesions were found post mortem in the Ammon's horns (and elsewhere) of young patients with convulsions—changes which could not presumably have been present if destruction of the Sommer sector had occurred at birth. Although the relative importance therefore of birth injury as against post-natal influences may still be undecided, Cavanagh and Meyer (1955) found that the incidence of Ammon's horn sclerosis was correlated with a history of convulsions first occurring in infancy or in early childhood.

In view of this, all the cases of epilepsy in Group 6 (fig. 13) in which the information was obtainable (a total of 27) have been charted

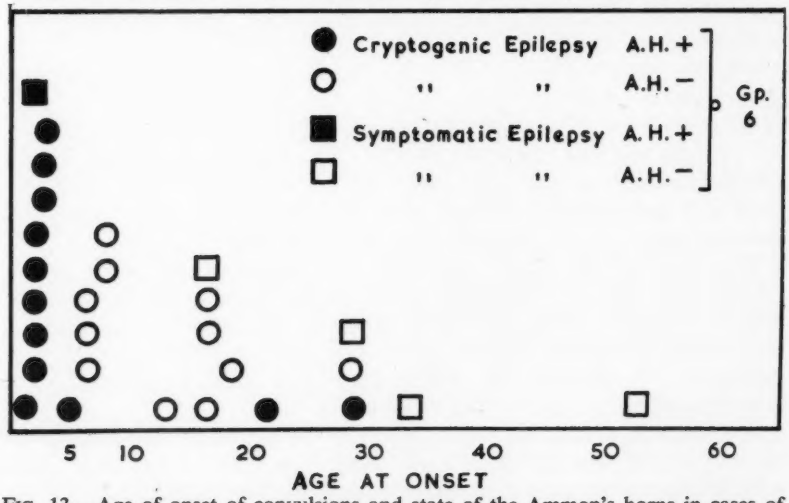


FIG. 13.—Age of onset of convulsions and state of the Ammon's horns in cases of epilepsy in Group 6.

to show the recorded age of onset of convulsions and the presence (A.H. +) or absence (A.H. —) of an Ammon's horn lesion. One case of temporal lobectomy with an Ammon's horn sclerosis has also been included in which the age of onset was $1\frac{1}{2}$ years.

Of the 15 cases in which either an acute lesion (in the 2 infants) or a sclerosis (13 adults) was present the onset of convulsions had been recorded as follows:

7 before or at the age of 2 years.
2 in infancy.
1 aged 5 years and 1 in childhood.
1 at 22 years and 1 at 29 years.
2 were unknown.

One case of congenital mental defect with epilepsy (Group 2, Case 2) had bilateral sclerosis.

So far every case examined in which the onset of fits was recorded as in infancy has shown either an acute lesion (and then death occurred in infancy) or a sclerosis, but the numbers are small.

In the case with onset of fits at the age of 29 the information was meagre and no details were known of the patient's childhood. In the case with onset at 22 years the patient's relatives were definite that "there was nothing in birth or childhood" to account for the epilepsy.

In the 15 cases without Ammon's horn sclerosis the earliest age of onset was 5, the oldest (a case of symptomatic epilepsy) was 53, the remainder being between 6 and 35.

Such findings would seem to strengthen the view that a connexion exists between the onset of convulsions in the early years of life and the eventual demonstration of an Ammon's horn sclerosis.

Whether the development of such a lesion depends as much upon the severity of the initial attack (i.e. onset in status epilepticus) as on the time of its occurrence (Cavanagh and Meyer, 1955) cannot be assessed from the present material, for although the age of onset of fits was nearly always recorded, or was obtainable, any more detailed analysis of the birth and early history of such patients, who for the most part have lived for many years in hospital, has not so far been possible.

This puts a limit to the scope of retrospective studies such as the present one, for while recent clinical and electrical work on epilepsy and the temporal lobes is largely based on the collection of detailed information about the early history and the adolescence of each new patient, it is usually the middle-aged and elderly, without such information, that come to the pathologist.

A similar restriction moreover seems to be placed on the analysis of future material, for the cases now being investigated from their onset will, in their turn, almost certainly outlive the investigators.

Finally, it should be emphasized that the majority of cases that are

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examined pathologically come either from mental hospitals or institutions and the relevance of the findings in these cases to the mass of epileptic patients living their life at home is not known.

Conclusions and Summary

The findings of the present investigation and the interpretation placed upon them may be summarized as follows:

(1) Out of 65 cases, selected only to avoid those patients with chronic organic disease of the brain, 5 (8 per cent) showed lesions of the Ammon's horns all of which were of recent onset. These were considered in each case to be related to terminal disease or to the development of severe hypoxia in the hours or days before death. In none of the 65 cases was Ammon's horn sclerosis found, and there was no evidence to suggest that this could be looked on as a common (or indeed as an uncommon) incidental finding.

(2) It was again confirmed that of those cases with organic disease of the brain the incidence of Ammon's horn lesions was essentially confined to the arteriosclerotic and the senile groups (including Alzheimer's disease) and to cases of general paresis, although very few cases of this were examined.

(3) The incidence of lesions in the group of epileptic patients was roughly the same as that in the senile and the arteriosclerotic groups, but differences both in the morphological appearances of the lesions and in the mechanism of their production, in so far as this is known, suggest that such lesions should not be grouped together indiscriminately. In the senile and arteriosclerotic cases the development of the lesion occurs during the last few years of life and is found in the presence of severe, widespread degenerative changes occurring throughout the brain.

In the senile these seem to be part of a generalized disintegration of cerebral tissue (although there is no explanation why this should be so strikingly intense in the hippocampus). In the arteriosclerotic the lesion is that of infarction related to vascular disease. Since, however, vascular change plays a part in the senile process no single explanation is likely to be adequate.

(4) In the adult cases of cryptogenic epilepsy the appearances are constantly those of a lesion of some considerable duration, and the evidence supports the view that this originates as the result of anoxia occurring in the early years of life, either as a birth injury or as the result of some upset in early childhood. Since convulsions, however, may themselves result in severe hypoxia they alone may account for the presence of a lesion.

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LEGENDS FOR PLATES

PLATE XIX

FIG. 1.—Normal Ammon's horn with the fields h1 to 5 indicated. (Cresyl violet, × 11.)

FIG. 2.—Group 1. Case 1. "Ischæmic change" affecting most of the nerve cells of the h1 field. (Cresyl violet, × 230.)

FIG. 3.—Group 1. Case 2. Part of h1 field of the Ammon's horn showing necrotic remnants of nerve cells and marked microglial proliferation. (Cresyl violet, × 230.)

FIG. 4.—Group 1. Case 3. Ammon's horn with pale, swollen h1 field and apparent disappearance of nerve cells. These are in fact still present but are shrunken and many have stained faintly. (Cresyl violet, × 11.)

FIG. 5.—Group 5. Case 1. Infiltration by tumour tissue of the medial edge of the Ammon's horn and of the adjacent small vessels with swelling and necrosis of the h1 field, marked nerve cell loss and much microglial proliferation. (Cresyl violet, × 11.)

PLATE XX

FIGS. 7 and 8.—Examples of classical Ammon's horn sclerosis from cases of cryptogenic epilepsy, showing the almost complete loss of nerve cells, apart from h2 and the dentate gyrus, and an even distribution of glial nuclei throughout the affected area. (Cresyl violet, × 11.)

FIG. 9.—A small circumscribed scar in h1/h2, the result of an infarct due to arterio-sclerosis. (Cresyl violet, × 11.)

FIG. 10.—The pale, moth-eaten appearance of the h1 field, with decimation of the nerve cell population in a case of senile dementia. (Cresyl violet, × 11.)

FIG. 11.—Neurofibrillary tangles and formation of senile plaques at subicular end of h1 field. (Cresyl violet, × 210.)

FIG. 12.—Coronal cut through a temporal lobe from a case of cryptogenic epilepsy, showing a sclerosed Ammon's horn with adjacent areas, both of older damage and of recent hæmorrhage. (× 1·3.)

XUM

PLATE XIX

FIG. 1.

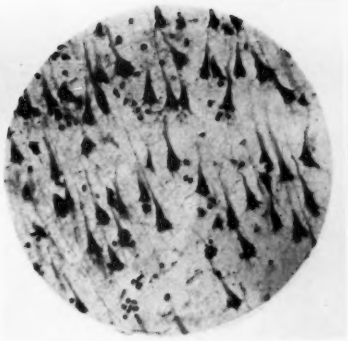

FIG. 2.

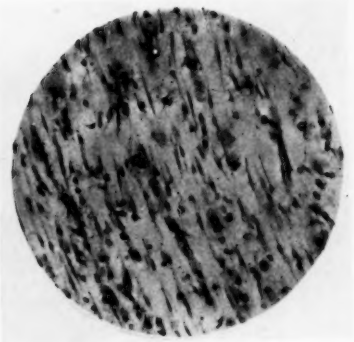

FIG. 3.

FIG. 4.

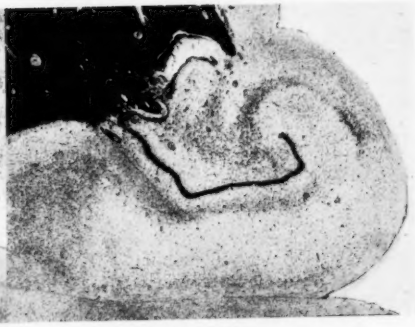

FIG. 5.

To illustrate article by J. A. N. Corsellis.

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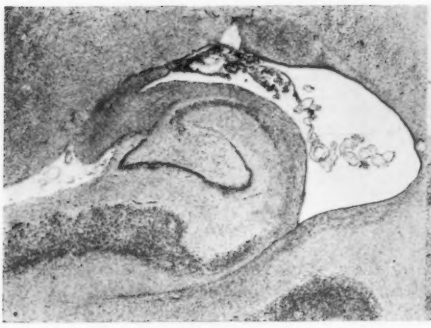

FIG. 7.

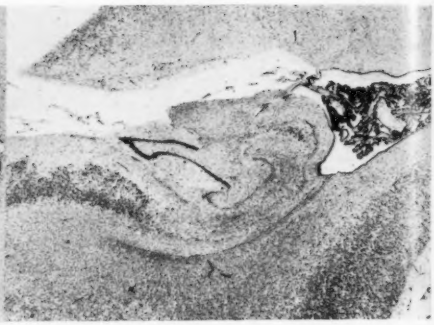

FIG. 8.

FIG. 9.

FIG. 10.

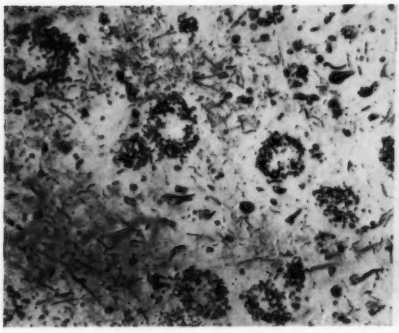

FIG. 11.

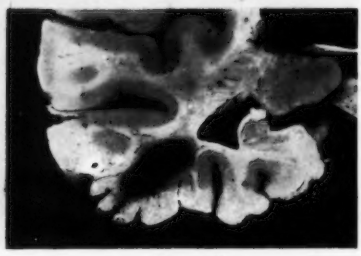

FIG. 12.

To illustrate article by J. A. N. Corsellis.

NECROTIZING ENCEPHALITIS

BY

AGATHA R. CRAWFORD AND F. LENORE J. ROBINSON

Northern Ireland Fever Hospital, Purdysburn, Belfast

DURING the last few years three unusual cases of encephalitis have come to post-mortem in this hospital, and within the same period two similar cases have died in other hospitals in Belfast. In describing these cases together we do not mean to imply that they necessarily belong to one ætiological group, but they do possess certain features in common which, so far as we know, have not been seen in the post-mortem material in this province, and which have not commonly been reported in the literature. The condition is essentially one of extensive necrosis in the cerebral cortex, with a lesser degree of damage in the basal ganglia and brain-stem. Intranuclear inclusion bodies have not been found in any of the cases.

CASE HISTORIES

Case 1.—*K. M., female, aged* 30 *years.* Duration of illness twenty-two days.

The patient was admitted on November 26, 1951. She had been taken seriously ill on the evening of admission with a feeling of generalized weakness quickly followed by a unilateral convulsion (site unknown) and deep coma. There was a history of a single "fit" one year previously.

On admission she was pyrexial and there was neck stiffness. The pupils were equal and reacted to light. The fundi were normal. Lumbar puncture yielded a blood-stained fluid containing 9 white cells per c.mm., sugar 117 mg. per cent, protein 80 mg. per cent, and with a negative Wassermann reaction. Two days later a second specimen was withdrawn; this was clear and under normal pressure.

Six days following admission she had another fit, this time localized to the left face and left hand, and followed by flaccidity of the left arm. She remained comatose, incontinent, and pyrexial throughout this period, although the level of consciousness varied.

On December 3, 1951, she was removed to the Neurosurgical Unit of the Royal Victoria Hospital for more specialized investigation. There she continued in a state of coma. No muscle wasting was evident, but the tone was increased in both arms and legs. The eyes wandered independently; the pupils were contracted, equal, and irregular, but both reacted to light directly and consensually. The corneal reflexes were present. Burr holes were made in the fronto-temporal region on both sides. There was no increase in tension, and both dura and brain appeared normal. The frontal and temporal regions were needled and no abnormality found. Cerebrospinal fluid was withdrawn from both lateral ventricles and found to be normal.

A few days later, while still in a state of coma, the patient suffered from frequent "Jacksonian" fits, sometimes affecting the left and sometimes the right side of the body.

XUM

At first they were minor, but later became so severe that continuous intravenous medication was required to control them. She remained in this state until her death on December 17, 1951.

An EEG report of December 5, 1951, stated: "There is no alpha rhythm. A generally abnormal record showing diffuse slow activity of high amplitude particularly anteriorly and more on the left side. Short waves are seen in frontal regions, and are more focal in the right frontal region. No clearly cut wave forms seen. Conclusion: A generally abnormal record. There is an epileptogenic focus in the right frontal region."

Pathological findings.—A *post-mortem* (Ref. No. A 9264) was done about four hours after death. The body was that of an obese woman. Naked-eye and microscopic examination of the thoracic and abdominal organs revealed only some œdema, patchy atelectasis, and terminal pneumonia in the lungs.

Brain: The brain was very soft, with flattened convolutions, bilateral grooving of the uncal regions by the edge of the tentorium cerebelli, and cerebellar coning into the foramen magnum. When examined after fixation, the meninges over the vertex were seen to be moderately opaque and thickened. On section, the softness of the cerebral hemispheres was even more apparent than in the fresh brain. There was patchy vascular congestion, and in the cortical grey matter, which appeared uneven in depth, there were groups of petechial hæmorrhages. In one segment of the convolution F2 (left) the grey matter was swollen to form a softening 1 cm. in diameter.

Microscopical examination.—Cerebral cortex (fig. 1)*:* The arachnoid was thickened by fibrous tissue, and the subarachnoid space was full of fibroblasts, dilated blood vessels, and an exudate consisting mainly of large mononuclears with a few plasma cells and lymphocytes. In many areas the cortex was completely necrotic. It was stuffed with compound granular corpuscles and some polymorphs; no nerve cells could be identified in it. The cortical vessels were greatly congested, but there was no inflammatory infiltration of their walls and no thrombosis. The perivascular spaces were full of large mononuclears and plasma cells, with an occasional polymorph. Capillaries were conspicuous because their endothelium was greatly swollen. In the subcortical white matter there was a widespread diffuse increase of astroglial nuclei. The vessels here also were cuffed by chronic inflammatory cells, including many plasma cells. There were one or two small foci of hæmorrhage, and one small vessel was necrotic and full of thrombus, but there was no inflammatory exudate around it. There was no calcification in any of the necrotic areas of cortex.

Cortical lesions were most marked in the frontal, parietal, and temporal regions. In the occipital regions destruction was much less and there was a diffuse increase of astrocytes and microglia. These sometimes formed "glial nodes" which may indicate focal destruction of nerve cells.

Basal ganglia: These were relatively mildly affected and showed no areas of complete necrosis. There was marked perivascular cuffing, diffuse proliferation of glia, and in the adjacent white matter a few necrotic venules with surrounding "ring hæmorrhages" were present.

Brain-stem, at level of seventh nucleus: There was no massive necrosis but some nerve cells were shrunken and hyperchromatic with occasional satellitosis. Perivascular cuffing was present and there was diffuse gliosis with a few "glial nodes." The arachnoid membrane was slightly thickened.

Cerebellum: This showed only the loss of a few Purkinje cells.

Sections of the brain were stained by Lendrum's method and neither in these nor in the H. and E. sections were intranuclear or intracytoplasmic inclusion bodies found.

No material was available for virus studies.

Case 2.—*A. H., male, aged* 34 *years.* Duration of illness eleven days.

On March 21, 1953, the patient developed diarrhœa and vomiting which lasted for

twenty-four hours and was accompanied by pains in his legs. He returned to work for a short time but on April 4, 1953, his terminal illness began with frontal headache which persisted for two days when he became pyrexial and had slight neck stiffness. He was treated with intramuscular penicillin and oral sulphonamide and was admitted to the Northern Ireland Fever Hospital on April 8 because of a gradual worsening of his condition.

On examination here he was found to be drowsy, inattentive, and had slight neck stiffness. There was no muscle weakness, and apart from the eyes wandering independently no abnormality of the central nervous system could be detected. Superficial and deep reflexes were present. The ocular fundi were normal.

Lumbar puncture on admission yielded a clear fluid with 156 white cells per c.mm. (98 per cent polymorphs), sugar 71 mg. per cent and protein 87 mg. per cent, and a repeat puncture twenty-four hours later gave a similar result.

In twenty-four hours he had worsened considerably, being deeply unconscious with marked neck stiffness. The visual axes were divergent and the eyes continued to wander separately. The left plantar response became extensor. He remained in this state without localizing signs until his death on April 14, with the exception of a transitory period of some hours when he became lucid and could answer questions. Throughout his stay in hospital his temperature varied between 100° F. and 105° F.

Serological tests (Central Health Laboratory, Colindale) were negative for influenza A and B, and for Q fever, lymphocytic choriomeningitis, leptospirosis, and mumps.

Pathological findings.—A *post-mortem* (Ref. No. A 10373) was performed about fourteen hours after death. The only important findings in the organs of the thorax and abdomen were severe œdema of the lungs and terminal pneumonia.

Brain: The brain presented a most striking appearance. The right temporal lobe was sharply marked off from the rest of the brain, being swollen, red, and covered by a conspicuous network of dilated pial vessels; it was very soft but not fluctuant. Otherwise the brain appeared normal to the naked eye except for a slight grooving of the uncal region on both sides by the edge of the tentorium cerebelli. After fixation, the brain was sliced in the coronal plane. The right temporal lobe was very soft, with blurring of the normal pattern.

Microscopical examination.—Cerebral cortex (fig. 2)*:* In sections of the right temporal lobe there was extensive necrosis of the grey matter. The nerve cells had disappeared and the tissue contained large numbers of compound granular corpuscles. Small patches of fresh hæmorrhage were present, sometimes with a necrotic arteriole in the centre. The vessels were congested and were surrounded by a thick cuff of lymphocytes. One or two vessels showed infiltration of their walls by polymorphs, plasma cells, and large and small mononuclears; there was no thrombus or necrosis of their walls, and these cells were probably merely passing out from the blood. A few large mononuclears and lymphocytes were present in the subarachnoid space over the necrotic areas. Towards the edge of the cortical necroses there was survival of the subpial layer with no infiltration of it by inflammatory cells. From the outer granular layer inwards there was complete necrosis of the grey matter.

Sections of other areas of the cerebral cortex did not show necrosis of the nerve cells but there was widespread congestion and cuffing of vessels by lymphocytes with an occasional large phagocyte which contained brown granular pigment giving a negative Prussian blue reaction. An occasional nerve cell was shrunken and surrounded by a group of oligodendrocytes. There was glial proliferation with the formation of "glial nodes." A few mononuclear cells were present in the subarachnoid space.

Basal ganglia, mid-brain, pons, and medulla: These were all only slightly affected. Cuffing of vessels by lymphocytes was present and occasional foci of astrocytic and microglial proliferation.

XUM

The *cerebellum* appeared normal.

The upper end of the *cervical spinal cord* showed only a mild degree of perivascular cuffing by lymphocytes.

Sections of cerebral cortex in necrotic and non-necrotic areas and of basal ganglia were stained by Lendrum's method for inclusion bodies. No intranuclear inclusions were found in these sections or in any of those stained by H. and E. A few round hyaline bodies staining bright red with phloxine were found lying loose in the ground substance in and near necrotic areas. The largest was about 8 μ in diameter, but most were smaller.

Sections stained by Loyez' method demonstrated complete loss of myelin in the necrotic areas, while in other areas of the brain there was no demyelination.

A sample of cerebral cortex was frozen and sent to Dr. F. O. MacCallum of the Virus Reference Laboratory, Colindale. A suspension of this was inoculated on to tissue cultures of monkey kidney cells, but no cytopathic changes were detected during two passages.

Case 3.—*P. J. McF., male, aged* 59 *years.* Duration of illness twenty-two days.

For two days prior to his admission to hospital on June 14, 1953, the patient complained of nausea followed by a persistent headache. On the day after admission he had a shivering attack lasting a few minutes and followed by a deep sleep. Later he became unconscious. There are no further details available until June 21, when he was transferred to the Neurosurgical Unit of the Royal Victoria Hospital. He was found to be conscious but disorientated, with a marked degree of neck stiffness. The only other signs referable to the central nervous system were spasticity of the right arm, and some degree of increased tone in the right leg. The plantar responses were flexor.

A cerebrospinal fluid taken on admission was clear, under normal pressure, with 90 white cells per c.mm. and protein 95 mg. per cent. A repeat lumbar puncture on the following day gave a similar picture.

At this time he was thought to have an intracranial abscess, and was treated vigorously with antibiotics but without response. Deterioration continued, and on June 30 bilateral parietal burr holes were made. Through these the pia arachnoid was seen to be thickened, and the brain somewhat yellow. A ventriculogram was normal. No radical surgery was attempted. He died on July 4, 1953.

An EEG report on June 22 stated: "A generally abnormal record with diffuse theta activity. No definite focus or asymmetry noted but at times the right frontal region, and at other times the left posterior central regions seem more affected. Conclusion: A generally abnormal record of no lateralizing value."

Pathological findings.—A *post-mortem* (Ref. No. 10542) was performed on the day of death. The brain only was available for examination. It showed opacity of the meninges, especially over the fronto-parietal regions. The cerebral convolutions were flattened and there was slight uncal herniation on the right side. When the brain was sliced coronally, the lower half of the cerebral hemispheres was unusually soft but there were no gross hæmorrhages.

Microscopical examination.—Cerebral cortex: There was slight fibrous thickening of the arachnoid membrane with occasional calcified arachnoid granulations; this is unrelated to the present disease process and probably of little significance. The subarachnoid space contained a filmy network of fibroblasts, many macrophages, and a few red blood cells, plasma cells, and lymphocytes. The veins on the surface of the brain were greatly congested but their walls were normal, and they contained no thrombus.

Some rather sharply demarcated areas of cortex were completely necrotic. There was loss of all nerve cells, and the brain tissue was replaced by an œdematous spongy material full of compound granular corpuscles, a few of which contained brown

granular pigment which gave a negative Prussian blue reaction. Plasma cells were also present. The capillaries, arterioles, and venules had greatly swollen endothelial cells and some contained thrombus. In places the necrosis extended into the subcortical white matter. The latter contained many small hæmorrhages; one or two of these showed a small necrotic and thrombosed vessel in the centre but although these vessels were infiltrated by red blood corpuscles there was no inflammatory reaction in or around them. The subcortical white matter also contained an excess of astroglial nuclei. One block of cortex showed at the bottom of a sulcus an abrupt change from the complete necrosis described above to relatively unaffected tissue, which showed only satellitosis around a few of the nerve cells. There was also a diffuse increase in glial nuclei. The perivascular spaces were full of lymphocytes and a few large mononuclears. The subarachnoid space overlying this relatively normal cortex contained only a sparse infiltration of lymphocytes and large mononuclears. Other blocks of cortex from different areas showed the same patchy distribution of necrotic areas rather sharply demarcated from surrounding surviving tissue. There was no calcification in this brain.

Basal ganglia: The thalamus showed some patchy necrosis. Elsewhere there was chromatolysis in nerve cells, a diffuse increase of astroglial nuclei, and marked perivascular cuffing. Several small arteries in and near the globus pallidus showed "pallidal siderosis."

Mid-brain and pons: There was a little patchy necrosis in the mid-brain in the neighbourhood of the substantia nigra. Elsewhere there was perivascular cuffing, diffuse increase of glial nuclei, but no loss of nerve cells.

Medulla: This was normal except for a mild degree of perivascular cuffing.

Cerebellum: A few Purkinje cells had disappeared; otherwise nothing abnormal was seen.

No intranuclear or intracytoplasmic inclusion bodies were found in any of the sections.

Sections of cortex, basal ganglia, pons, mid-brain, and medulla were stained by Loyez' method for myelin. There was complete destruction of myelin sheaths in the areas of frank necrosis, but in other parts of the brain there was no demyelination.

No material was available for virus studies.

Case 4.—*S. McK., male, aged* 2 *years.* Duration of illness fifty days.

This boy was admitted to hospital on April 17, 1955, with a history of intermittent vomiting and fretfulness of three days' duration. On the day of admission he was pyrexial and had had three generalized convulsive attacks.

On examination, the child was flushed, febrile and had a tachycardia. Some fine moist sounds were heard at the right base and because of these findings he was diagnosed and treated as a basal pneumonia. There were no signs referable to the central nervous system.

On the next day he became drowsy, and this was quickly followed by a series of convulsive episodes which were extremely difficult to control. Slight neck stiffness now appeared and a C.S.F. at this time showed a white cell count of 109 per c.mm., the sugar being 90 mg. per cent and the protein 20 mg. per cent. The ocular fundi were normal. Two subsequent C.S.F.s were similarly abnormal. The Wassermann and Kahn tests on the blood were negative as was the Wassermann reaction of the C.S.F.

His further progress was that of deepening unconsciousness, of continuous fits, and the development of a spastic paraplegia with marked opisthotonos. After about three weeks the spasticity disappeared but the child remained drowsy with occasional twitchings. In this state he remained until his death on June 3, 1955. He was pyrexial throughout his time in hospital.

XUM

No virus serology was done on this patient. The mother's serum was tested about a year later by the dye and complement-fixation tests for toxoplasma antibodies and both were negative.

An EEG report of June 19 stated: "Patient unconscious during recording. The pupils were dilated and did not respond to light. His record is dominated by diffuse low amplitude slow activity 1 c/s. Frequent left-sided sharp epileptic waves were seen. These occurred in runs at remarkably regular intervals, one every two seconds approximately. No definite focus, but they seem to arise from the left parietal region. Conclusion: a very abnormal record with epileptic features."

Pathological findings.—A post-mortem (Ref. No. A12119) was performed thirty-six hours after death. The lungs were œdematous with small subpleural areas of collapse. Microscopically the kidneys showed cloudy swelling of the convoluted tubules, and in the pyramids there were a few necrotic tubules with calcium deposited in the epithelium. There was a mild degree of centilobular fatty change in the liver. Otherwise the thoracic and abdominal organs were normal.

Brain: The cerebral hemispheres were the seat of an extensive destructive process which had caused marked softening especially of both temporal lobes which were almost fluctuant (fig. 3). The frontal and occipital poles were of normal consistency. The mid-brain, pons, and medulla looked almost normal except for a little blotchy discoloration. No cerebellar coning or other evidence of increased intracranial pressure was present.

Microscopical examination.—Cerebral cortex: Several sections from different areas showed the same picture, of extensive tracts of necrosis in which all nerve cells had disappeared. The tissue was a thin sponge full of compound granular corpuscles and astrocytes, many of the latter greatly swollen to form *gemästete* cells. The vascular channels were conspicuously dilated and were thickly cuffed by lymphocytes, plasma cells, and a few large mononuclears. There were no hæmorrhages and the walls did not show necrosis, thrombosis, or inflammation of their walls. The necrotic areas contained much calcium, deposited in granular masses of varying size (fig. 4). Where calcium was abundant there were occasional multinucleate giant cells with up to eight nuclei; many of these cells contained granules of calcified material. In adjacent white matter a few capillaries and arterioles had granules of calcium deposited along the basement membrane and in the media. In some necrotic areas, the layer immediately beneath the pia was very œdematous and contained microglial and astroglial cells, but the inner layers of the cortex were much more heavily infiltrated and contained much calcium. Here and there necrosis extended deeply into the subcortical white matter.

Occasional curious bodies (fig. 5) were seen in the sections of necrotic cortex. Each consisted of a vaguely outlined mass about 30 μ in diameter, and in the centre was a group of small round or oval sharply-defined bodies which stain deeply with hæmatoxylin, are blue in a Giemsa preparation and Gram-negative when stained by Brown's method. In some areas up to four occurred in one low power field, while in other necrotic areas there were none. They did not resemble any fungal or protozoal organism known to us, and were thought to be some form of cellular degenerative change in the *gemästete*-type astrocytes. No toxoplasma organisms were identified in the sections of this brain.

The meningeal reaction over the necrotic cortex was only slight; the vessels were greatly congested and there were sparsely scattered large and small mononuclears in the subarachnoid space.

Basal ganglia: There was a little patchy necrosis in the basal ganglia. Elsewhere in this region there was œdema and a diffuse increase of astrocytes and microglia. Some nerve cells had swollen acidophil nucleoli, and some showed disintegration and

neuronophagia. The vessels in the basal ganglia and surrounding white matter were congested and their perivascular spaces were filled with lymphocytes and a few plasma cells and large mononuclears. Part of the circumference of a small vein was necrotic and infiltrated with polymorphs, while the perivascular space round the rest of the wall contained the usual mononuclears.

Medulla: The nerve cells were intact and showed only minor changes, possibly due to post-mortem autolysis. There was a diffuse increase of astrocytes and some microglial proliferation, most marked in the grey matter. The vessels and meninges were normal.

Upper cervical spinal cord: This was similar to the medulla.

No intranuclear inclusion bodies were found either in the H. and E. sections or in sections from various parts of the brain stained by Lendrum's method. In or near necrotic areas of the cortex there were some small round brightly eosinophilic hyaline bodies similar to those in Case 2. The largest was about 8 μ in diameter. Most were lying loose in the tissue but in a few small glial cells of unidentified type the cytoplasm was crowded with similar tiny bodies. They stained pale pink with Giemsa.

Loyez' stain demonstrated complete disintegration of the myelin sheaths in the necrotic areas with bulbous swellings and fragmentation where destruction was less advanced. In other parts of the brain there was no demyelination.

No material was available for virus studies.

Case 5.—R. C., male, aged 12 years. Duration of illness fifty-two days.

This child was admitted to the Northern Ireland Fever Hospital on July 1, 1955, with a history of two days' illness. It began when he was sent home from school because he looked unwell; that evening he had difficulty in speaking and swallowing. He spent a restless night. In the morning he developed twitching on the left side of his face which persisted at intervals throughout the day. In the evening he was admitted as a suspected case of polioencephalitis.

On examination he was found to be alert and co-operative but his attention wandered easily, and he was never quite still, his arms and legs continually performing short, jerky, purposeless movements. There was some weakness of the left arm. His speech was slurred and almost unintelligible, and swallowing was difficult. There was weakness of the left face, palatal movement was sluggish, while the tongue was almost completely immobile. The ocular fundi were normal. There were no meningeal signs and his admission temperature was 101° F. Analysis of the C.S.F. at this time showed 29 white cells per c.mm., sugar 59 mg. per cent, and protein 17 mg. per cent. X-rays of skull and chest were normal.

On the day following admission he had a "Jacksonian" fit involving the left side of his face, without loss of consciousness. This occurred again five days later but was more extensive involving the left arm and in passing off left a more obvious weakness in that limb. At this time he became markedly ataxic, and was unable to walk without assistance. All reflexes were brisk and the plantar responses were flexor.

During the next two weeks he deteriorated slowly, becoming dull, mute, apraxic, and incontinent. Then came a remission with general improvement in all faculties. This lasted for three weeks and was followed by a sudden relapse in which myoclonic jerkings in all limbs became a feature. His terminal state was that of post-encephalitic Parkinsonism with mask-like face, rigid limbs and tremor of the hands. He had a fluctuant pyrexia throughout his entire illness with a daily maximum of 100° F. to 103° F.

Serological tests were done at the Central Health Laboratory, Colindale and were negative for leptospira, mumps, lymphocytic choriomeningitis, influenza, Q fever, psittacosis, and streptococcus M.G.

XUM

Pathological findings.—A post-mortem (Ref. No. A12263) was performed about twenty-one hours after death.

The body was very emaciated. Apart from œdema and bronchopneumonia in the lungs, with mild tracheitis and œsophagitis, the only finding of note was the presence in the adrenal cortex of focal necroses infiltrated by polymorphs.

Brain: This was apparently normal naked-eye, and there was no flattening of the convolutions or other evidence of increased intracranial pressure. After a week's fixation the brain was sliced in the coronal plane. On both sides there was an area of complete necrosis involving the lower part of the post-central gyrus and extending inwards towards the internal capsule (fig. 6). The frontal and occipital lobes were practically normal naked-eye with only some congestion here and there. The temporal lobes, basal ganglia, and brain-stem showed blotchy reddish staining and small foci of hæmorrhage, but no massive necrosis.

Microscopical examination.—Cerebral cortex: Sections from the lower end of the post-central gyrus showed large areas of completely disintegrated tissue with no surviving nerve cells. This change extended in some parts into the subcortical white matter. The tissue was a loose sponge of compound granular corpuscles and swollen astrocytes with scattered lymphocytes and plasma cells. Here and there were lakes of plasma. The vessels were dilated, but their walls were normal and they did not contain thrombi. They were cuffed by a thick zone of mononuclear cells. Sections stained for fat by Fettrot stain demonstrated that around the edge of the necroses there was a widespread dusting of fat particles with a few clumps presumably within phagocytes, and in this zone the vessels were cuffed by lymphocytes and plasma cells. Where necrosis was complete, however, practically all the fat was within phagocytes which were so numerous as to form solid sheets in places and the vessels were cuffed largely by the same fat-laden cells. A large proportion of this lipoid material was in the form of doubly refractile crystals, presumably cholesterol esters.

A striking feature of the brain of this case was the presence of very large numbers of multinucleate giant cells. They measured up to 25 μ in diameter and had up to ten nuclei arranged usually in a ring round the periphery. Some contained irregular masses of dull pink material surrounded by a clearer halo and some of these could be identified as phagocytosed cells. Examination with crossed Nicol prisms did not reveal any doubly refractile material. In sections stained by Ziehl-Neelsen's method no acid-fast bacilli could be found, and staining by Brown's method for organisms and by Giemsa failed to show any pathogen. There was no calcification. Some areas of necrosis contained none of these giant cells, others only a few scattered ones, while here and there, even in cortex which otherwise showed only slight gliosis and perivascular cuffing, there were miliary granulomata composed of giant cells and a few lymphocytes (fig. 7).

Sections of cortex in and near necrotic areas were stained by Lendrum's method for inclusion bodies. No intranuclear inclusions were found in these sections nor in those stained by H. and E. or Giemsa. Large numbers of round hyaline eosinophilic bodies similar to those in Cases 2 and 4 were found (fig. 8), mainly lying loose in or near necrotic tissue. The smallest were often in clumps and in a few cases could be seen to be intracytoplasmic, probably in astroglial cells.

One hyaline body similar to those seen in Case 4 (cf. fig. 5) was also found in necrotic cortex in this case.

The meninges over the necroses showed only slight changes: extreme congestion of the otherwise normal vessels, and a few large and small mononuclear cells in the subarachnoid space.

Basal ganglia: These showed no massive necrosis, but there was a diffuse increase of nuclei, both astrocytic and microglial, and the vessels were heavily cuffed by

lymphocytes and plasma cells. Some nerve cells in the basal ganglia showed satellitosis by oligodendroglial cells.

Mid-brain: The nerve cells were largely intact. There was marked increase of micro- and astroglia with the formation of "glial nodes" which may indicate focal loss of nerve cells. Perivascular cuffing was severe.

Cerebellum: There was a slight increase of nuclei in the white matter and a few small vessels showed a minor degree of perivascular cuffing. The nerve cells appeared normal and no inclusion bodies were found.

Lower end of medulla: The meningeal vessels were congested and there were patches of lymphocytic infiltration in the subarachnoid space. The medulla itself showed widespread damage mainly in the grey matter. The nerve cells had survived, but there was an increase of nuclei, mostly microglial, to form "nodes." There was severe perivascular cuffing by lymphocytes and a few larger mononuclears. The vessel walls themselves were not inflamed and there was no thrombosis, but in some very small vessels the endothelium was swollen so that the lumen appeared occluded.

Spinal cord: A section from the upper end of the cervical cord was normal except for a small vessel in one anterior horn which had a few lymphocytes and large mononuclears in the perivascular space. Sections from several levels of the rest of the cord were all normal.

Sections of brain stained by Loyez' method showed complete destruction of myelin sheaths in areas of frank necrosis, but apart from this there was no demyelination.

Portions of brain were frozen and sent to Professor G. W. A. Dick for virus isolation studies. The report is as follows: "0·03 ml. of a 10 per cent crude suspension of brain was inoculated intracerebrally into three-week-old mice. Another group of mice of the same age were inoculated intraperitoneally with 0·5 ml. of this suspension. The mice were observed for five weeks and then discarded. No pathogenic organism was isolated."

Discussion

The name "encephalitis" is applied to a very heterogeneous collection of diseases. In some the cause can be shown, for example in toxoplasmosis, lymphocytic choriomeningitis, psittacosis, etc., but frequently no ætiological agent can be demonstrated and the cases can only be classified with the help of explanatory adjectives which are a summary of the histological features. Nevertheless, they do fall into several fairly well-defined groups as described by Greenfield (1950):

(1) *Acute polioclastic type*, in which the grey matter of the cerebral cortex bears the brunt of the damage.

(2) *Acute hæmorrhagic leuco-encephalitis* (Baker, 1935; Hurst, 1941; Henson and Russell, 1942), in which there is inflammation in and around vessels with hæmorrhages, damage being maximal in the white matter. This condition may be an allergic phenomenon allied to acute disseminated encephalomyelitis (Russell, 1955).

(3) *Subacute inclusion body encephalitis* (Dawson, 1933, 1934; Brain, Greenfield and Russell, 1948; Foley and Williams, 1953), characterized by the presence of type A intranuclear inclusion bodies in the central nervous system.

(4) *Subacute sclerosing (leuco-) encephalitis* (van Bogaert, 1945), in

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which gliosis of the white matter is conspicuous. These are possibly examples of inclusion encephalitis in which inclusions are scanty.

The above classification is almost entirely histological, and by comparison with the encephalitides of known origin it has been assumed that they are likely to be of virus origin or (as in group 2) due to an allergic phenomenon in the central nervous system associated with a virus infection.

Our first 3 cases all fall into the first group of acute polioclastic encephalitis, with illnesses lasting twenty-two, eleven, and twenty-two days respectively, while Cases 4 and 5 are similar but of longer duration (fifty and fifty-two days). We may summarize the clinical aspects of the cases as follows. The patients were all resident in Northern Ireland, and there was no history of contact with similar cases or with sick animals. 2 were children and 3 were adults. None presented initially with an influenza-like illness as did some of the recorded cases (van Bogaert *et al.*, 1955). All had a sudden onset with headache, fits or coma except Case 4 in which three days of intermittent vomiting preceded the first convulsion. 3 cases were pyrexial throughout their stay in hospital, while records of the other 2 are incomplete. Neck stiffness was not always found initially, but was demonstrable at some stage in all 5 cases. All but Case 5 rapidly became unconscious and Cases 1 and 4 had persistent severe convulsions. Case 5 was characterized by myoclonic movements and mental deterioration finally progressing to a Parkinsonian state. The cerebrospinal fluids were abnormal in all, with raised cells, or increased protein, or both; unfortunately Lange curves were not done. Electroencephalograms on 3 cases were abnormal but none showed the periodic outbursts of activity described by Cobb and Hill (1950) as characteristic of subacute progressive encephalitis.

At post-mortem, the presence of a necrotizing encephalitis was not always appreciated in the fresh brain. The soft consistency of the cerebral cortex was usually marked with evidence of increased intracranial pressure due to swelling. After fixation and slicing of the brain, the patchy or widespread necrosis of the cerebral cortex was usually apparent. Histologically, the affected areas of cortex showed loss of all nerve cells, with destruction of the myelin sheaths, and replacement of the tissue by large numbers of swollen astroglia and microglial cells, many of the latter forming compound granular corpuscles full of lipoid. Varying numbers of plasma cells and lymphocytes were also present, and the overlying meninges were similarly infiltrated. Vascular damage was relatively slight, there being only a few small venous thromboses and necrotic arterioles surrounded by "ring hæmorrhages." These changes are not sufficiently widespread to have caused the necrosis. In this feature our cases differ from the condition which occurs in eastern and western equine encephalomyelitis in which inflammatory changes in the vessels are more prominent and have been thought, by Noran and Baker (1945),

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to be primary, the extensive cortical necrosis being considered secondary to vascular obstruction.

In our cases, other parts of the brain only rarely showed patches of frank necrosis (thalamus and mid-brain in Case 3, basal ganglia in Case 4), but there was widespread perivascular cuffing, and proliferation of astrocytes and microglia throughout surviving areas of cortex and in the basal ganglia and brain-stem. The cerebellum and spinal cord showed only slight changes.

Demyelination was not a feature of these cases, being only present in the necrotic areas. Gliosis was not marked and was proportional to the duration and to the degree of neuronal damage.

All our cases were carefully searched for intranuclear inclusion bodies, but none were found. In Cases 2, 4, and 5 eosinophilic hyaline bodies were found free or occasionally within the cytoplasm of glial cells. They are similar to those described in many of the recorded cases of encephalitis and are probably degenerative products of no ætiological significance.

Case 4 was unusual in that the necrotic cortex contained large amounts of calcium. No toxoplasma was seen in this brain, and the mother's serum contained no toxoplasma antibodies. Extensive calcification has also been recorded in Japanese B virus encephalitis (Zimmerman, 1946) and in occasional cases of other types of encephalitis, so that although its presence suggests toxoplasmosis it is by no means pathognomonic.

Case 5, of fifty-two days' duration, was unlike the others in that multinucleate giant cells were a prominent feature and often formed miliary granulomata. No bacterial, protozoal or fungal pathogens were found.

None of our 5 cases showed any myocarditis, and apart from pulmonary œdema and terminal pneumonia there were no important pathological changes in the thoracic and abdominal viscera.

We have not found in the literature many cases resembling those reported here. Greenfield (1950) reported 2 rather similar cases (Nos. 2 and 9 in his acute polioclastic series) with illnesses lasting eight days and three weeks respectively, and he also mentions that occasional cases of subacute progressive polioclastic encephalitis without inclusion bodies may occur. van Bogaert, Cordier, and Henneaux (1955) have recorded a case of acute necrotizing encephalitis in a woman of 58 who died after fifteen days, and whose brain showed extensive cortical necrosis, no intranuclear inclusions, and slight vascular changes. They had previously encountered another similar case.

Of recent years the various types of encephalitis in Britain have presented as sporadic cases, and this makes it difficult to assess what range of clinical and pathological features can be attributed to one ætiological agent. This also makes adequate virus studies often impossible as the cases may be missed during life and even at post-mortem, so that by the time histological examination shows the condition to be an encephalitis

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the chance of a more exact diagnosis has been lost. Since it is only by more complete serological and virus isolation tests that such cases can yield the information needed to elucidate this group of diseases, it seems still worth while to record even incomplete studies of unusual examples of encephalitis in the hope that they may serve as a reminder that such cases are by no means rare in the British Isles.

SUMMARY

Five unusual cases of encephalitis occurring in Northern Ireland during the last few years have been reported. All showed severe cortical necrosis, and a lesser degree of damage in the basal ganglia and brain-stem. In one case calcification was a prominent feature; another was unusual in showing large numbers of multinucleate giant cells. No intranuclear inclusion bodies were found.

ACKNOWLEDGMENTS

Our grateful acknowledgments are due to Dr. F. F. Kane, the late Mr. C. A. Calvert, Mr. A. R. Taylor, and Dr. O. D. Fisher for access to the clinical records, and to Dr. G. F. W. Tinsdale for helpful criticism. We wish to thank Professor J. H. Biggart for permission to use the facilities of his department and for advice and help. We are grateful to Dr. F. O. MacCallum and to Professor G. W. A. Dick for virus serological and isolation tests. We are also indebted to Mr. D. McA. Mehaffey, A.R.P.S., for the photography.

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LEGENDS FOR PLATES

PLATE XXI

FIG. 1 (*Case* 1).—Cerebral cortex, showing loss of nerve cells, and profuse cellular infiltration of cortex and subarachnoid space. H. and E. × 125.

FIG. 2 (*Case* 2).—Cerebral cortex, showing necrosis, and intense cellular infiltration of the deeper layers. H. and E. × 100.

FIG. 3 (*Case* 4).—Coronal section of brain, showing extensive necrosis of cerebral cortex with some patchy extension into subcortical white matter and basal ganglia.

PLATE XXI

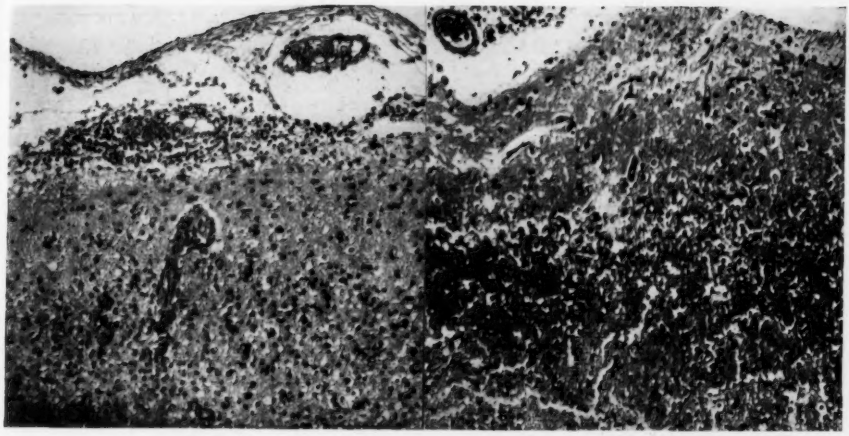

FIG. 1.

FIG. 2.

FIG. 3.

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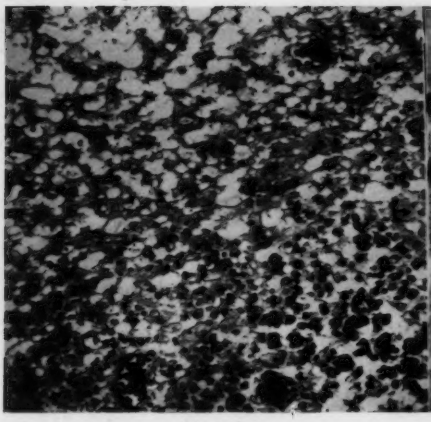

FIG. 4.

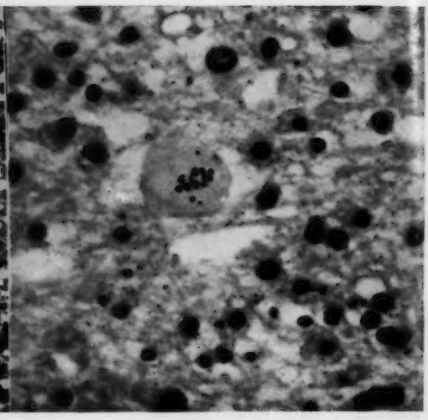

FIG. 5.

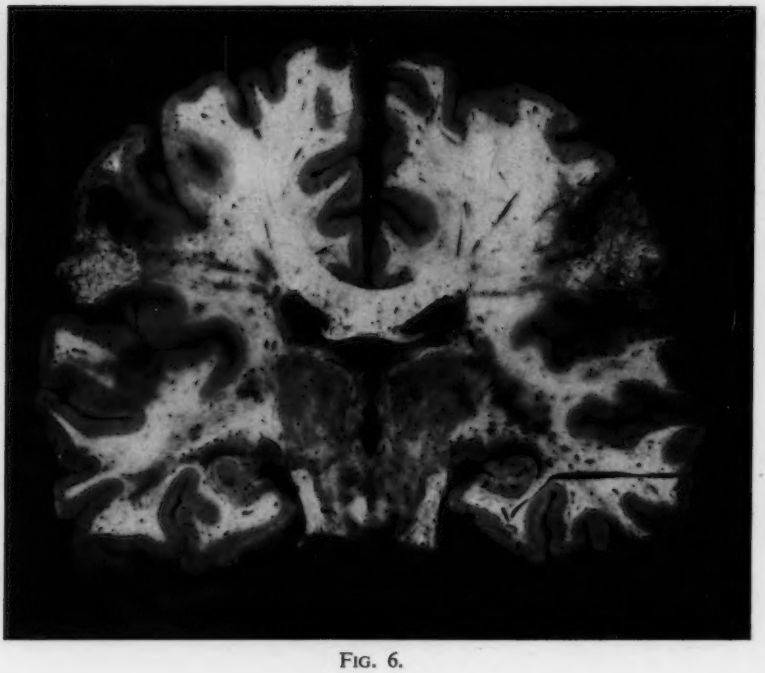

FIG. 6.

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PLATE XXIII

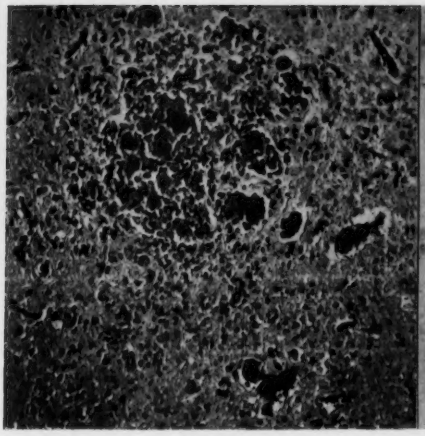

FIG. 7.

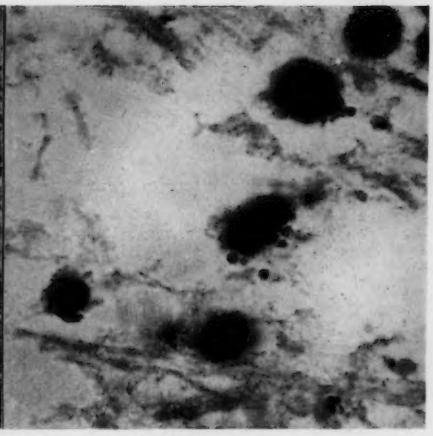

FIG. 8.

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PLATE XXII

FIG. 4 (*Case* 4).—Necrotic cerebral cortex, with œdema, cellular infiltration, and (R. bottom corner) calcium deposits. H. and E. × 225.

FIG. 5 (*Case* 4).—Hyaline body with granules, in necrotic area of cerebral cortex. Lendrum's stain. × 650.

FIG. 6 (*Case* 5).—Coronal section of brain showing bilateral areas of complete necrosis in lower end of postcental gyrus, also widespread patchy damage of more recent date.

PLATE XXIII

FIG. 7 (*Case* 5).—Miliary granuloma with giant cells, in cerebral cortex. H. and E. × 100.

FIG. 8 (*Case* 5).—Intra-cytoplasmic inclusion bodies, in necrotic cortex. Lendrum's stain. × 2200.

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AN INVESTIGATION OF SOUND LOCALIZATION IN PATIENTS WITH NEUROLOGICAL ABNORMALITIES

BY

E. GEOFFREY WALSH

Department of Physiology, University of Edinburgh

THE ability to localize sounds has often been investigated, particularly by psychologists and there exists a number of reviews that serve as a guide to the voluminous, but widely scattered, literature on this subject (*see* S. P. Thompson, 1882; Ferree and Collins, 1911; Watt, 1917; Ogden, 1924; Woodworth, 1938; Licklider in Stevens, 1951, and Piéron, 1952). In spite of this intensive study the parts of the brain that are concerned are not definitely known. A number of attempts have been made to approach this problem in animals (Table I) but the sounds have been carried to the ears through the air in the normal way ("diotically") and it is therefore not clear to what extent the responses have been reactions to binaural differences of intensity. Certain varieties of mammals have been shown to respond to spatial aspects of sound after removal of the cerebral hemispheres (Table I) but the evidence as

TABLE I.—EFFECT OF NEUROLOGICAL LESIONS ON ABILITY OF ANIMALS TO LOCALIZE SOUND

A. The Effect of Bilateral Decortication on Reflex Movements of Head or Ears Towards Source of Sound

Investigator(s)	*Year*	*Animal*	*Responses*
Karplus and Kreidl ..	1914	Monkey	No evidence of localization: startle response to loud sounds
Dusser de Barenne ..	1920	Cat	Localization demonstrated
Rothmann	1923	Dog	Localization demonstrated
Schaltenbrand and Cobb	1930	Cat	Localization demonstrated. "While awake she was extremely sensitive to sound, the breath of the examiner was sufficient to cause a rotation of the head"
Bard and Rioch ..	1937	Cat	Localization demonstrated. "She would often turn and walk or even run toward the source of a light, whistle or of a scraping noise"
Smith*	1939	Guinea-pig	Localization demonstrated

*These observations were incidental to other work and the experimental details are scanty.

TABLE I—*contd.*

B. The Effect of Division of Mid-brain (Decerebration) on Reflex Movements of Head or Eyes Towards Source of Sound

Investigators	*Year*	*Animal*	*Lesion*	*Responses*
Forbes and Sherrington	1914	Cat	Bilateral	No unequivocal evidence of localization but animals pricked up ears
Bazett and Penfield ..	1922	Cat	Bilateral	No evidence of localization but animal would raise its head if scratching noise was made
			Unilateral	"Hearing was acute and sounds were well localized"

C. The Effect of Cerebral Lesions on Sound Localization Using Condition Reflex Techniques

Author	*Year*	*Animal*	*Lesion*	*Conditioned response*	*Responses*
Bikov (quoted by Pavlov)	1927	Dog (1 animal)	Section of corpus callosum	Salivation	Not elicited
Girden ..	1939	Dog	Section of corpus callosum	Movement of fore-limb	Elicited
Pennington	1937*a*	Rat	Bilateral temporal lobectomy	Maze running	Loss of pre-op. habit
Pennington	1937*b*	Rat	Bilateral temporal lobectomy	Maze running	Post-op. learning normal
Neff ..	1951	Cat	Bilateral temporal lobectomy	Food selected from a box	Present but poor

D. The Effect of Bilateral Destruction of the Inferior Colliculi on Reflex Movements

Authors	*Year*	*Animal*	*Responses*
Ferrier and Turner ..	1901	Monkey	"As regards hearing, when a bunch of keys was jingled to right or to left, a reflex movement of the corresponding auricle was observed"

to man suggests that deprivation of the fore-brain prevents all such responses. Thus Edinger and Fischer (1913) recorded a case of an infant that lived for three and a half years and which at post-mortem was found to lack cerebral hemispheres. They remark that "Wenn etwas mit lautem Geräusch hinfiel, wurde wiederholt ein Zusammenschrecken beobachtet, aber sonst niemals etwas wahrgenommen, was auf Hören hinwies. Die Mutter hat sich viele Mühe gegeben, das zu ermitteln." Similar observations were made by von Monakow (1926) on a microcephalic idiot the fore-brain of which weighed only 25 grammes. Very loud sounds elicited a startle response but otherwise it showed no response whatsoever to sounds: "Auf laute Schalleindrücke (Händeklatschen, Schlüsselklirren usw.) erfolgt keine Reaktion, auch keine Bewegung der Augen in der Richtung des Reizes. Sobald man aber

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einen Metalldeckel an den Kopf des Patienten anlegt und dann Schall auslöst, zuckt Patient zusammen."

Quite apart from these considerations there are certain advantages to be gained from studying neurological aspects of sound localization in man as well as in animals. With human subjects the conditioning procedures that may be needed in animal work are replaced by brief periods of instruction or training and there is no difficulty in delivering the stimuli by headphones ("dichotically"), a procedure that enables various of the factors concerned to be studied in turn by the use of suitable controlled electrical currents. A number of clinical reports dealing with sound localization have been traced (Table II) but the

TABLE II.—PREVIOUS CLINICAL INVESTIGATIONS OF EFFECT OF LESIONS OF NERVOUS SYSTEM ON SOUND LOCALIZATION

Author(s)	*Year*	*Mode of stimulation*	*Lesion*	*Results*	*Comments*
Greene ..	1929	Diotic and dichotic	Acoustic neuroma	Normal	
Söderberg ..	1931	Dichotic	Bilat. labyrinthine loss of function (1 case)	Normal	Hearing was unaffected
Güttich ..	1939	Diotic	Bilat. labyrinthine loss of function (4 cases)	Inaccurate	Selection of clinical material severely criticized by Diamant 1946
Diamant ..	1946	Diotic	Bilat. labyrinthine loss of function (3 cases)	Normal	
			Cerebellum		
Meyer ..	1912	Diotic	Bilat. cerebellar abscess (1 case, boy)	Good localisation	"Schnell und exakt"
Goldstein ..	1925	Diotic and dichotic	Unilateral cerebellar lesions (3 cases)	Bias to side of lesion	Goldstein believed that muscle tone influenced sound localisation*
Greene ..	1929	Dichotic and diotic	4 glioma 2 glioma 1 medulloblastoma	Normal Impaired Impaired	One quite unable to use time differences
			Cerebral Cortex		
Gordon Holmes	1919	Diotic	Unilateral lesions of angular gyrus (8 cases)	Normal	Visual disorientation present

*Ryan and Schehr (1941) were unable to verify Goldstein's contention that the position of the eyes influences auditory localization in a systematic manner.

TABLE II—*contd.*

Greene ..	1929	Dichotic and diotic	About 25 assorted cerebral lesions.	Normal	
			13 other cerebral lesions	Impaired	Ability to use time intervals completely lost only in one case (temporal hæmangioendothelioma)
Hemphill and Stengell	1940	Diotic	Pure word deafness (1 case)	Abolished?	
Akelaitis ..	1942	Diotic	Section of corpus callosum	Normal?	No detailed statement of results
Parkes Weber	1947	Diotic	Extensive bilat. vascular lesions (1 case)	No satisfactory lateralization	L and R confused in other ways
Ross and Fountain	1948	Diotic	Excision of right fronto-parieto-temporal cortex (1 case)	Normal	He could lateralize sound perfectly whether the stimulus came from one side alone or from both sides simultaneously
Wortis and Pfeffer	1948	Diotic	Right hemisphere lesion (1 case)	Correct when source right sided, poor when left sided	Old right mastoidectomy. Left homonymous hemianopia
Denny-Brown, Myer and Horenstein	1952	Diotic	Right parietal lesion (1 case)	Normal for single source	With bilat. stim. opp. each ear she always erroneously said that the direc. of sound was from the right

Investigations of Sound Localization in Blind Persons

Authors	*Year*	*No. of blind subjects*	*Results*
Dufour (*see* Hayes, 1941, p. 22)	18	—	Superior to normal
Griesbach	1899	28	No superiority
Krogius (*see* Hayes, 1941, p. 27)	1905	20	Superior to normal
Seashore and Ling	1918	16	No superiority†
Bernovits	1936	40	Superior to normal

†Seashore and Ling noticed some increase in sensitivity of the blind group but the changes were small (average difference 0·1 degree) whilst the variation between different blind and different sighted people was substantial. Any effect of blindness was so small as to be negligible in view of the other factors affecting directional sensitivity.

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results do not agree well with one another. Greene (1929) working at Cushing's neurosurgical clinic was the most systematic of the earlier workers but he did not have the advantages that have accrued in this type of work from the use of electronic devices. Accordingly the present study was undertaken and a variety of tests have been employed to investigate different aspects of this spatial sensitivity.

The difference in the time at which sound reaches the two ears is known to be of great importance in man for the lateralization of transient sounds and accordingly the use of this cue was one of the first problems to be tackled. Electronic apparatus was devised to enable the ears to be stimulated by clicks without being disturbed by differences of intensity. Such stimuli are more simple than those arising naturally, at least indoors, for numerous reflections occur and a sound once generated may reverberate around the room many times before it sinks in intensity below the level of the auditory threshold. The brain is provided with a mechanism whereby the first signals to arrive at the two ears contribute most effectively to localization; the later repetitions are largely neglected (Wallach, Newman and Rosenzweig, 1949). Accordingy it seemed advisable to investigate this "precedent effect" for it was possible that the mechanisms concerned had different loci, or susceptibilities, from those tested in the binaural time difference procedure. Furthermore the ear is, at times, exposed to sinusoidal wave forms of long duration rather than to transients. Accordingly an investigation has also been made of the ability of neurological patients to respond to binaural differences of phase, using pure tone stimulation. No observations have been made upon the effect of lesions on the ability to utilize binaural intensity differences but investigations were made upon the nature of the diffraction pattern surrounding the human head that have a bearing on the interpretation of certain experiments.

Binaural cues by themselves do not allow sounds to be localized in the vertical plane; the auditory data must be linked with estimates of head movement (Young, 1931). It seemed possible that neurological lesions might interfere with vertical localization even when localization in the horizontal direction was still possible. Accordingly some observations have been made using natural sources of sound. Another approach also was made to this problem—the "Twin Speaker Test." If the observer is placed midway between two loudspeakers energized from the same electrical supply any sound produced may be referred to a point above the head.

Methods

Binaural Time Differences

The apparatus is shown diagrammatically in fig. 1. The circuits delivered electrical pulses to a pair of crystal headphones so that one of the ears received a click an instant before the other. The times quoted in this paper refer to the interval

between the two clicks although it is arguable that the physiological stimulus should be regarded as being twice as large because the method of testing involved a reversal of the sequences of the clicks. This inversion of the order was accomplished by a cross-over switch at a point in the circuit before the stages which determined the final form of the pulses; the order could, therefore, be altered without changing the shape, or size of the pulse reaching the headphones. The pulses rose abruptly reaching their maximum in 25 μsec, thereafter they slowly decayed, reaching the baseline after a further 2·1 msec. The decay was not strictly exponential for the headphones offered a non-ohmic load to the apparatus but any tendency of the electrical pulses to generate a decrementing oscillatory state was obviated by damping resistors in parallel with the receivers. The mechanical stimulus delivered to the hair cells of the cochlea was, however, probably oscillatory, for the middle and inner ear mechanisms are not critically damped (*vide* Békésy in Stevens, 1951). It was possible to vary the relative intensity of the pulses to allow for differences in the sensitivity of the ears. The signals were monitored on an oscilloscope and the time-intervals were measured by comparison with the output of a low frequency oscillator. The results of checking the frequency of this oscillator against a crystal controlled standard and a consideration of the error involved in measurements on the face of the cathode ray tube suggested that inaccuracies of up to 20 per cent occurred in the estimation of the time-intervals.

The patients were given a practice period to accustom them to the procedure and, at this time, they were told on which side to expect the clicks to be heard. During the test they were usually required to indicate, by pointing, the side from which the sound appeared to come; this procedure was found to be more reliable than depending upon a verbal response. At each time interval that was used a series of six trials was undertaken. The stimuli, right first, or left first, were presented in a random sequence. If the subject was correct in all six responses it may be assumed that the nervous system was sensitive to that time difference for the probability of such an event occurring by chance is low (1 in 64).

Precedence Effect and Twin Speaker Test

To investigate the precedence effect the same electronic apparatus was used but the electrical pulses supplied moving coil loudspeakers which were placed at equal distances (1 metre) on either side of the patient's head (fig. 3). Each ear was thus stimulated by two pulses in succession, one from each loudspeaker. In addition the sound reverberated around the room for an unknown period. This reverberation came from walls more distant than the loudspeakers and three of the four walls of the room had been treated with sound absorbing tiles ("Celotex"). This uncontrolled reverberation was probably of little importance; normal subjects could correctly indicate the speaker that received the first of the pulses under conditions where the reverberation must have been substantially greater (speakers some metres apart, in an untreated room).

For the twin speaker test (fig. 4) the two units were connected in parallel. They were normally placed on either side of the subject about 1 metre from his ears, but the position was in no way critical as long as the two distances were equal. The speakers were supplied with pulses from a neon relaxation oscillator or from a circuit that was interrupted by a clockwork contactor.

Phase Differences

A phase-shift network consisting of a condenser and resistance combination was used to alter the phase of pure sine waves by 90 degrees. The sine waves were derived from a low frequency oscillator; a frequency of 250 c/s was chosen because this value falls well in the range within which the auditory system is known to be sensitive to phase differences (Hughes, 1940). Potentiometers were used to adjust

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the strength of the signal passed through the phase-shift network to one of the headphones until it was equal to that passed through a simple resistance to the other. A reversing switch was arranged so that at will either the right or the left headphone would lead the other as to phase. The signals were monitored on a cathode-ray tube. A double pole switch, silent in operation, was connected across the headphones, and by this means the patient was exposed to the signal for not more than a few seconds at any given trial. This procedure was adopted to minimize "attunement" (James, 1936).

Diotic Stimulation

For comparing the ability to localize sounds in the vertical and horizontal planes simple arrangements sufficed. A miniature musical box movement was employed as a source; it gave rise to a tune as the metal reeds that it contained were successively thrown into operation by the clockwork mechanism. The subject was blindfolded and pointed to a position on a metre stick that appeared to correspond with that of the sound source (fig. 5).

Results

Lateralization of Sound

(1) Retention of Auditory Local Sign in Patients with Cerebral Lesions

A normal person can readily identify which of his ears is being stimulated when a sound is presented to one only. It appeared possible that neurological lesions might interfere with this ability without interrupting the interpretation of sound patterns. Accordingly a number of patients were investigated, clicks being led to one headphone or to the other in a random way. The patient was asked to indicate on which side he heard the noise. The data are summarized in Table III. Many of the lesions were extensive, and in certain of the patients disturbances of the body schema were evident. Nevertheless none of the patients had any difficulty in performing the test satisfactorily. It may be assumed that all areas of the cerebral cortex were implicated in one or other of the patients.

Another patient, diagnosed as suffering from "pure word deafness" is of some interest by way of contrast: H. H. W., aged 42, was examined in the Morriston Hospital, Swansea, by courtesy of Dr. F. Hamdi. Six months previously the patient had suddenly become unable to understand speech although he still heard sounds.

On examination he had a slight, but definite, right-sided spastic hemiparesis. No other neurological abnormalities were detected. He was able to perform arithmetical addition and multiplication. He found his way in the ward without difficulty. He could draw objects from memory and could also copy drawings normally. He could express himself well and had no difficulty in naming common objects. Occasionally he inverted the order of words but normally his speech was grammatically correct. Clinically his ability to hear appeared to fluctuate. An audiogram revealed only a moderate hearing loss that was approximately equal on the two sides. The loss at 250 c/s was 20 db, it increased to a maximum of 35 db. at 2,000 c/s. Many subjects with peripheral deafness of corresponding or greater degrees, although "hard of hearing," do not display the striking difficulty in interpreting speech that

TABLE III.—TESTS OF AUDITORY LOCAL SIGN (ABILITY TO INDICATE CORRECTLY EAR STIMULATED) IN PATIENTS WITH CEREBRAL LESIONS

Hospital No.	*Sex*	*Age*	*Diagnosis*	*No. of trials*	*No. incorrect*
C 12465	M	29	Hæmorrhage into R. temporal lobe from middle cerebral aneurysm	5	1
C 12563	M	58	R. temporal astrocytoma	8	0
C 12195	M	47	L. temporal glioblastoma	4	0
C 12487	F	61	L. temporal glioblastoma	5	0
C 12564	M	17	L. temporal astrocytoma	4	0
C 12916	F	64	L. temporal meningioma with hæmorrhage into the lobe	5	0
C 12602	F	33	R. temporal astrocytoma	6	0
C 17708	M	51	L. parietal astrocytoma	6	0
C 12476	M	42	L. parietal malignant hæmangioendothelioma	8	0
C 12326	M	6	R. parietal astrocytoma	6	0
C 4408	M	12	R. parietal lobe ependyoma	4	0
C 172	F	33	L. parieto-occip. memingioma	4	0
C 12157	M	36	R. parieto-occipital astrocytoma	8	0
C 11400	F	51	L. parieto-occipital glioglastoma	4	0
C 12480	M	17	L. precentral memingioma	7	0
C 12816	M	27	R. frontal astrocytoma..	6	0
C 12664	M	46	R. frontal cholesteatoma	4	0
C 11361	M	57	R. inf. frontal glioblastoma	6	0
C 11684	M	32	Bifrontal malignant astrocytoma	3	0
C 13007	F	51	Glioma R. ant. thalamus	7	0
C 5982	M	54	Tumour of septum pellucidum	5	0
38776	F	14	R. hemispherectomy	11	0

this subject showed. The clicks available for the binaural time interval test were 35 db above threshold for a normal observer. To subjects with normal hearing they were loud but for this subject they were so close to threshold that testing was not possible. When tested with pure tones he had some difficulty in determining whether the sound was coming from the right or the left headphone and he sometimes thought it came from both sides when it came from one only. Later it became quite clear with continued testing that, by concentrating intensely, he was able to lateralize the note correctly.

These findings may be contrasted with those of Hemphill and Stengel (1940). They, also, investigated a case of pure word deafness and remarked: "It is not certain if he could not perceive direction but he did not react to it." That auditory local sign is retained in many neurological conditions is of importance. If it were lost it is inconceivable that sounds could be correctly lateralized.

(2) BINAURAL TIME DIFFERENCES

A. Normal subjects.—Preliminary observations were made on a small number of normal young adults. When the time-interval was shorter than about 2·5 msec. the subject had the sensation of a single sound and it was with this experience that the observations recorded in this section were principally concerned. The click was normally heard as though it

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came from a region that was close to the ear which was stimulated first. Nevertheless, it would be wrong to suppose that all responses to the second of the pulses was totally occluded by the arrival of impulses in the nervous system resulting from its predecessor; the loudness of the sound was greater than that resulting when the stimulus was allowed to reach one ear alone. It is apparent that binaural summation of loudness is not limited to sounds which occur exactly synchronously in the two ears. On reversing the sequence of the clicks it was sometimes noticed that not only the laterality, but also the quality of the sound changed; with short time-intervals it was difficult to know to what extent the more sophisticated subjects responded to a change of apparent position, and to what extent to a difference of timbre. An analogous change in quality has been noticed by Jeffress (1948*b*), when with a pure note the phase difference between the supply to the two ears is altered.

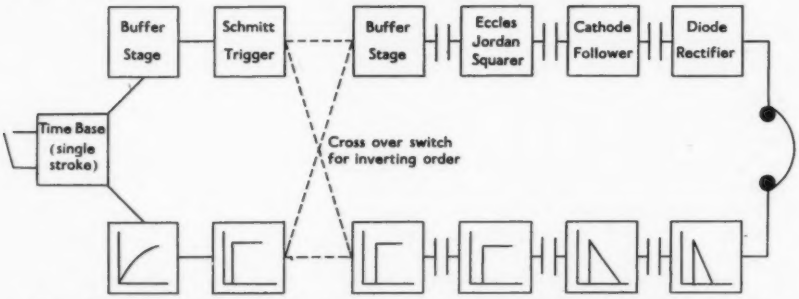

FIG. 1.—Schematic representation of apparatus used for production of pulses used in *binaural time difference tests.* A simple time base, triggered from a manually operated switch fed two chains of valves which shaped the pulses. The time interval was determined by the Schmitt triggers; by adjustment of the operating conditions of one of these the delay could be altered. The cross-over switch that followed enabled either headphone to receive the first pulse to be produced. Lower half of figure indicates wave shapes at different stages.

Occasionally it was found that the person localized the phantom source to an unusual site, such as the occiput of the skull; this sometimes appeared to be the result of an incorrect adjustment of the intensities of the clicks delivered to the two ears. No special heed was paid to the introspective reports of the subjects and attention was directed rather to ascertaining whether or not the nervous system could detect binaural time-differences at all; this limitation must be borne in mind in interpreting the data.

Many workers have been interested in determining the least time interval that the auditory system can detect; there has been, however, no general agreement as to the values. Aggazzotti (1911) reported that time-intervals of 70 μsec could be used and similar values were

obtained by Trimble (1928) and by Wallach, Newman and Rosenzweig (1949). Langmuir, Schaefer and Ferguson (1944) found one observer ("A") who could detect time differences of 20 μsec for pulses and even smaller values of delay for random noise and pure sine waves. Wilcott (1955) was interested in the "angular displacement threshold of simulated auditory movement" and his data suggest that the auditory system may be sensitive to time-differences of 40 μsec or less whilst Klumpp (1953) who used electrical delay lines to obtain binaural time differences quotes a threshold of 12 μsec. The reasons for these discrepancies are far from clear but it must be pointed out that the production of suitable stimuli is fraught with pitfalls. In the older work mechanically-operated contacts were often used and cathode-ray tubes were not available to determine the nature of the pulses that had been produced. Other work has depended upon acoustical delay pathways and here differences in intensity and timbre are liable to be produced. Even electrical delay paths may not be immune from these difficulties. Certainly values of 3 μsec quoted by Kerr (1943) and 30 msec. by Kreidl and Gatscher (1923), a difference of 10,000 fold, must be regarded with the greatest suspicion. In the present work normal subjects were found who were sensitive to 100 μsec and some subjects could improve upon this performance. No extensive survey was performed but values shorter than 60 μsec were rarely recorded and the lateralization was never vivid until the time interval amounted to several hundred microseconds.

B. *Cerebral lesions.*—The binaural time-difference test was applied to neurosurgical patients (Table IV). It was eventually possible to obtain a diagnosis that had been revealed by or confirmed at, surgical intervention in 20 of the patients tested in this way. In addition one case (No. 2, Table IV) is included in this series, although no operative procedure was undertaken, because the diagnosis appeared firmly established on other grounds. A number of the patients were moderately ill at the time of the investigation, and, for this reason, time-intervals were usually employed that would present no difficulty to a normal observer. No serious difficulty was encountered in getting the patients to comprehend the nature of the test even though, in some cases, the intellectual powers had been seriously restricted by disease. Commonly there was some evidence of aphasia.

The lesions were scattered in different parts of the cerebrum and some were deeply situated, nevertheless all of the patients succeeded in utilizing binaural time differences. The series included no cases of fully developed Gerstmann's syndrome or of acute confusional states. Post-mortem examination of the brain was possible in 2 of these cases. One of these patients (No. 20, Table IV) was a widow aged 51 who was initially believed from the clinical history, and, independently, from the electroencephalographic evidence to have a frontal tumour. She died in

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coma after surgical intervention and at post-mortem a small hæmorrhagic glioma was found at the anterior tip of the thalamus on the right side. The second case that came to post-mortem (No. 4, Table IV) showed a large tumour classified as a glioblastoma multiforme invading the left temporal lobe. Professor G. J. Romanes kindly examined the

TABLE IV.—STEREOPHONIC TESTS (BINAURAL TIME DIFFERENCES) IN PATIENTS WITH CEREBRAL LESIONS

Hospital No.	*No.*	*Sex*	*Age*	*Diagnosis*	*Time intervals (μsec.)*	*Results + = successful − = unsuccessful*
C 12465	1	M	29	Hæmorrhage from R. temporal lobe from middle cerebral aneurysm	550	+
	2	M	34	War injury R. temporal lobe, depressed fracture and EEG spike focus	310, 170	+
C 12563	3	M	58	R. temporal astrocytoma	710, 650, 520, 200	+
C 12195	4	M	47	L. temporal glioblastoma	520, 210	+
C 12487	5	F	61	L. temporal glioblastoma	690	+
C 12564	6	M	17	L. temporal astrocytoma	690, 200	+
C 12916	7	F	64	L. temporal meningioma with hæmorrhage into the lobe	1,200	+
C 12602	8	F	33	R. temporal astrocytoma.	630,180	+
C 15300	9	F	44	Excision ant. $\frac{1}{3}$ l. temp. lobe in removal of medial sphenoidal ridge meningioma	1,400 690 380	+ + −
C 17708	10	M	51	L. parietal astrocytoma	570,170	+
C 12476	11	M	42	L. parietal malignant hæmangio-endothelioma	330	+
C 12326	12	M	6	R. parietal astrocytoma	930, 760, 170 70	+ −
C 4408	13	M	12	R. parietal ependymoma	320	+
C 12347	14	M	62	Lt. parietal metastasis from bronchogenic carcinoma	590	+
C 172	15	F	33	L. parieto-occipital meningioma	250 125	+ −
C 12157	16	M	36	R. parieto-occipital astrocytoma	290	+
C 12480	17	M	17	L. precentral meningioma	800, 300 135	+ −
C 12816	18	M	27	R. frontal astrocytoma..	760, 235	+
C 12664	19	M	46	R. frontal cholesteatoma	400	+
C 13007	20	F	51	Glioma R. ant. thalamus	540	+
C 5982	21	M	54	Tumour of septum pellucidum	790, 230	+

brain. On the left side the lateral geniculate body had been displaced upwards and was partly degenerate whilst the medial geniculate body could not be identified in the gross specimen. It was presumed that the cells of which it had been composed had degenerated owing to the interruption of the auditory radiations (Gudden's atrophy). It was clear that auditory impulses were not reaching the auditory cortex on the left side by their normal pathways, although it was just possible that the area was still being supplied by callosal fibres from the opposite hemisphere.

It appeared likely from these studies that the auditory area of one hemisphere could be dispensed with without abolishing the ability to utilize binaural time-differences. Nevertheless it seemed worth while to obtain additional evidence upon this point. Dr. E. A. Carmichael very kindly arranged that a patient of his should be tested at the National Hospital for Nervous and Mental Diseases. This patient, a girl aged 14 (Cecilia S. No. 38776), had suffered from a left hemiplegia and from very frequent fits from the age of 1. In July 1952 a right hemispherectomy had been performed by Mr. W. McKissock and at the time of testing one year later she had been, since the operation, completely free of attacks. She was sensitive to time-intervals of 190 μsec, 410 μsec and 2·5 msec. but unable to use an interval of 125 μsec. These results agreed with the patient's own impression, that she could, under natural conditions, tell the direction of a source of sound.

The preservation of binaural hearing in such a patient is of greater importance than in a normal person on account of the hemianopia. This was illustrated by another patient who also had undergone hemispherectomy. She was investigated, again through the kindness of Dr. E. A. Carmichael (T. P. 22684, aged 21). She was unfortunate enough to have also a severe deafness of obscure cause affecting the left ear. Although she could tell to which side a click was delivered she apparently appreciated the left-sided stimuli only because they stimulated sensory endings of the ear-drum itself. She was unable to use binaural time differences. The combination of blindness to the right side with a loss of stereophonic sense meant that she was essentially without warning of dangers approaching from one side. She remarked spontaneously that she had several times been knocked down by bicycles in the street.

Another patient was a boy aged 5¼ years old who had undergone hemispherectomy (C 11190) three and a half years before. The operation had successfully alleviated the fits, which had previously been troublesome but the boy was an imbecile and could not comprehend the simplest commands. The localization of sound was tested by observing his reactions to a whistle and toy trumpet. It was uncertain whether he could localize a sound then it was made immediately above his head.

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He was observed, however, to turn to the side of a sound on a number of occasions. These observations, showing that lateralization was possible, support the evidence already presented.

C. *Brain-stem lesions.*—Three patients who had lesions of the brain-stem were studied. One Pole aged 29 (C 3738) had a tumour at the level of the superior colliculi which gave rise to a loss of pain, temperature and position sense on the opposite side of the body. Evidently the spinal and medial fillets had been interrupted. There was additionally a mild, contralateral hemiparesis. This man performed successfully at 440, 250 and 175 μsec but failed at 62 μsec. In the second patient the lesion also appeared to lie in the tegmentum of the mid-brain but more medially. The man, aged 21 (MN 573) had a left-sided third-nerve palsy and a Parkinsonian tremor of the head and right arm and leg. Sensibility did not appear to be disturbed. The lesion appeared to be a mesencephalitis and responded to penicillin. At the time of testing he was speechless but could point with his left hand to side on which he heard the sound. He performed satisfactorily with intervals of 1 msec, 200 μsec and 120 μsec. The third patient (MN 585) aged 53 suffered from an external ophthalmoplegia, being unable to look at will from side to side and having also severe limitation of vertical eye movements. Whilst no definite diagnosis was established it was suggested that she suffered from Wernicke's encephalopathy, for with the institution of vitamin-B therapy her condition improved. Although "dizzy" and being liable to vomit on sitting up she successfully utilized binaural time-differences of 2·0 and 1·0 msec although she failed at 200 μsec.

D. *Atresia of external auditory meatus.*—Especial use of the sound localization apparatus in the blind may perhaps lead to some improvement in performance over normal (Table II) but what would happen if the neural apparatus for localizing sounds was not used in childhood and was brought into play only in adult life? It might be supposed that an alert adult confronted with a fresh sensory experience could rapidly learn its significance, but could he experience the sensation at all? Would neural channels unused for years remain patent?

An attempt has been made to approach these problems by investigating the responses of a subject who had a congenital atresia of the right external auditory meatus in association with a malformation of the pinna (fig. 2). The subject (R. J. C.) was a medical student aged 20 when tested. The hearing in the left ear was normal whilst he believed that very loud sounds were capable of stimulating the right ear; it is usual with such anomalies of the external ear to find that the inner ear itself is normal, although the ossicles may be deformed (Shambaugh, 1950; Woodman, 1952). In this subject hearing must normally be monaural and he stated that when attempting to localize a sound (e.g. an aeroplane,

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FIG. 2.—Deformed pinna of right ear.

or someone calling him) he had been in the habit of looking first in the direction from which the sound appeared to come and then in the opposite direction for he was aware that the initial impression was often incorrect.

These difficulties might have been expected but they are worthy of note in view of the report of Angell and Fite (1901). These observers investigated a subject who had been deaf in one ear since childhood and found that localization of sounds could still be achieved (cf. Starch, 1908). Clearly observations of the effect of moving the head upon the loudness of the sound may render monaural localization possible. Another potentially useful cue is the change in quality of familiar sounds with alteration of bearing. Corresponding to the greater obstruction that the head offers to high frequencies transient sounds may be of different quality on the two sides. In general steeply rising wave fronts will suffer most. Lord Rayleigh (1926) noticed that the tick of a clock sounded different when his back rather than his face was towards it, a difference which he ascribed to the pinna.

In testing this subject the intensity of the pulse delivered to the right ear was increased substantially, but with the range available it was impossible to make the clicks appear of equal loudness on the two sides and they differed also in quality. This lack of balance probably accounts for the fact that, with the binaural test, he noticed that when the right ear received the first click a double sound was heard—one click in each ear. When the left ear was stimulated first the phantom sound was single and was referred to the left ear. The subject was sensitive to

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time difference of 2·1 msec. and 980, 630 and 340 μsec whilst he was unable to use an interval of 230 μsec.

E. *Severe deafness.*—In this last investigation the existence of substantial differences between the performances of the two ears did not prevent the utilization of binaural time differences. One other case also illustrates this point. The patient was a woman of 28 who suffered from left-sided deafness due, it was thought, to Ménière's disease. The hearing loss increased steadily from a mere 7 db at 50 c/s to 40 db at 3,000 c/s. The binaural test was performed with the amplitude of the pulses to the left ear larger than, but not twice as great as, the pulse to the left ear. This provided only a very poor compensation for the deafness. Nevertheless the patient was able to utilize time-intervals of 2·4, 1·3 and 0·75 msec. although she could not deal with an interval of 350 μsec. These findings are in accord with the observations of other observers on the effect of altering the relative intensities at the ears of normal observers. Thus Langmuir, Schaefer and Ferguson (1944) note that "while unbalanced intensities in the two ears led to biased error's differences as much as 25 db often could be tolerated without losing binaural perception."

An even more striking example of the failure of deafness to disrupt the binaural time evaluation mechanism was afforded by a woman of 71 (Mrs. Mary S. Ward, 33, R.I.E.) who following a brief febrile illness was left with a severe bilateral nerve deafness. Similar cases have been described by others (*see* Heller and Lindenberg, 1955). The audiogram showed a hearing loss of 50 db at 128 c/s for the right ear and greater losses for all the other determinations. There was at least 70 db loss at all frequencies tested (128–8,192 c/s) for the left ear. She was able successfully to use time-intervals of 1·9, 1·2 msec but not 150 μsec. She could localize sounds such as the snapping of fingers to the right or left satisfactorily but with some bias to the right side. Nevertheless she had the greatest difficulty in understanding speech and sounds frequently were said to sound "metallic." When a pure note was switched from ear to ear it sounded of different quality on the two sides: binaural diplacusis.

F. *Para-acousis loci.*—Binaural time differences are of great importance in localizing sounds and these cases demonstrate how extremely resistant to damage is the neural mechanism. Complaints concerning an inability to localize sounds are rare, partly because of this resistance, partly because vision plays a dominant role under daylight conditions. One married woman aged 43 was encountered who had such a complaint. She had noticed that for three months she had tended to stagger to the right side when walking. For the same period she had had difficulty in concentrating and had suffered from headaches. No abnormal physical signs were elicited and a diagnosis of psycho-

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neurosis had been made by Dr. J. Stanton; factors predisposing to neurosis were elicited in the social history. She complained of being unable to tell the direction of sounds. Thus whilst cooking, sounds produced outside the house, such as the singing of birds, might appear to come from her kitchen utensils. At times she would turn away from the person who was addressing her and this she ascribed also to incorrect assessment of the source of sound. Nevertheless, she was able successfully to use time-intervals of 118, 393, 570 μsec and 1·4 msec.

Sound, like light, may be reflected and therefore erroneous conclusions may be reached regarding its source. Reflections are particularly likely to give trouble when, with sounds of relatively long duration, localization is based upon phase differences between the ears. Normal people sometimes localize sounds incorrectly and rarely remark upon the fact; the unusual feature of this patient was that she considered a few such instances worth mentioning. False localization may at times have disastrous results. Bowlker (1908) ascribed a collision between two ships, on one of which he was a passenger to "a mistake in judging of the direction of the foghorns," and owing to reflections from buildings it is often difficult to localize correctly car horns in towns (Perwitzschky and Bitterauf, 1934).

Gooddy and Reinhold (1952) described a case in which amongst other bizarre symptoms sound was localized to the wrong side of the body. "On being greeted by the examiner the patient looked searchingly for the source of the voice on the opposite side of the bed to which the examiner was standing." No definite diagnosis was established but there was strong presumptive evidence that much of the symptomatology was hysterical.

(3) Precedence and Phase Difference Tests

The *precedence effect* was effortlessly detected by normal people and all of the patients tested were successful (Table V). The lesions in 5

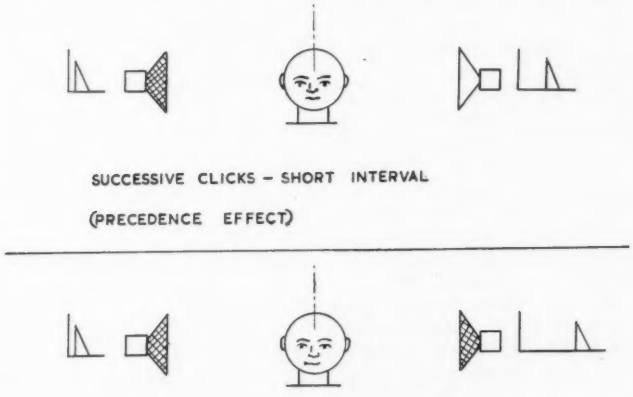
SUCCESSIVE CLICKS – SHORT INTERVAL
(PRECEDENCE EFFECT)
SUCCESSIVE CLICKS – LONG INTERVAL
(TWO SEPARATE SOURCES ARE PERCEIVED)

Fig. 3.—Arrangements for precedence test.

TABLE V.—PRECEDENCE TESTS

No.	*Sex*	*Age*	*Lesion*	*Time interval (msec.)*	*Result*	*Remarks*
C 15873	F	64	L. temporal and occipital metastases from bronchogenic carcinoma	7·9	+	Profoundly aphasic, R. homonymous hemianopia, proprioceptive loss R. limbs
C 16266	F	35	R. temporal lesion (vascular)	3·2	+	L. homonymous hemianopia
C 16872	M	29	L. temporal lesion (vascular)	0·8 3·2	+ +	Dysphasic, R. homonymous hemianopia
C 16651	F	33	Cerebral atrophy	2·4	+	L. homonymous hemianopia, L. proprioceptive loss
C 16735	F	56	Intraventricular meningioma	4·5	+	R. homonymous hemianopia, dyscalculia, dyslexia, and inability to draw from memory
C 15966	F	43	L. cystic temporal astrocytoma	3·1	+	Showed a bias to R. Thus when the L. stimulus was first she consistently said "both"
C 15777	M	58	L. temporal malignant astrocytoma	2·5	+	Showed a bias to L. Thus when the R. stimulus was first he consistently said "both"
C 15766	F	67	Tumour of Right Sylvian fissure reaching to insula	5·2	+	Disorientated for time
C 16217	M	39	R. fronto-temporal astrocytoma	3·2	+	
C 15888	F	40	R. frontal astrocytoma	2·2	+	
C 12498	F	33	R. frontal oligodendroglioma with extension through much of hemisphere	7·6	+	
C 4496	M	42	R. fronto-parietal astrocytoma	1·2	+	
C 16252	M	17	Traumatic lesion L. parietal lobe	3·3	+	Astereognosis R. hand, aphasia
C 16299	M	48	Glioblastoma deep L. parietal region	3·0	+	
C 15880	F	45	Cyst third ventricle	2·2	+	
MN 1061	F	41	Brain-stem lesion due to disseminated sclerosis. No conjugate deviation of eyes possible in horizontal plane	3·2	+	Bias to R. When L. stimulus was first the noise appeared to the patient to come from behind her

of the cases had given rise to a complete homonymous hemianopia; in 2 at least it is likely that the auditory zone was destroyed (C 16266 and C 16872).

Normal people often have to concentrate intensely to appreciate the effects of *phase differences*. Of the patients only one failed and she was disorientated and tired when tested (Table VI). 4 of the patients had findings that suggested that the auditory cortex had been destroyed, and yet were successful.

TABLE VI.—SENSITIVITY TO PHASE DIFFERENCES (90 DEGREES AT 250 c/s)

No.	*Sex*	*Age*	*Lesion*	*Sensitivity*	*Remarks*
C 15300	F	44	Partial L. temporal lobectomy for removal of spenoidal ridge meningioma	+	R. homonymous hemianopia
C 15410	M	57	Vascular lesions R. hemisphere	+	L. homonymous lower quadratic hemianopia and partial upper quadrantic defect
C 12498	F	33	R. frontal oligodendroglioma with extension through hemisphere	+	
C 15888	F	40	R. frontal astrocytoma ..	+	
C 15777	M	58	L. temporal lesion.. ..	+	
C 15346	F	15	R. temporal lobectomy for A-V aneurysm	+	L. homonymous hemianopia
C 16252	M	17	Traumatic lesion L. parietal lobe	+	Astereognosis R. hand, aphasia
C 16299	M	48	Glioblastoma deep L. parietal region	+ +	
C 16217	M	39	R. fronto-temporal astrocytoma	+	
C 16266	F	35	R. temporal lesion (vascular)	+	L. homonymous hemianopia
C 1120	F	39	A-V malformation in region of R. Sylvian fissure	+	L. upper quadrantic defect
C 15766	F	67	Tumour of R. Sylvian fissure reaching to insula	0	

(4) ROLE OF BINAURAL INTENSITY DIFFERENCES IN SOUND LATERALIZATION

Sources close to the head necessarily set up, for all frequency components, a significant intensity difference at the two ears due to operation of the inverse square law. For sources further away than 1 metre the law is less important for the differences are small and if they are less than $\frac{1}{2}$–1 db. little aid can be expected in the way of localization (Upton, 1936). For high frequencies (e.g. 5,000 c/s) the head itself casts a substantial sound shadow as Sivian and White (1933) have shown.

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It will be noted, however, that their data show a plot only for intervals of 30 degrees and not systematically for smaller values. Furthermore there are certain obscurities in the way that they calculated their data for they remark that "The curves shown were obtained not by averaging the three individuals' values for each angle, but by estimating a single curve to present the characteristic features of the individual curves."

The problem of the sound shadows cast by the head were investigated also by Wilska (1938) who used a plaster model and inserted microphones in place of internal ears. His data accord in the main with those of Sivian and White but again the angular differences were large. Wiener (1947) using a probe microphone measured the sound field at the ear drum for sources placed around the head. He used steps of 45 degrees.

These data apply to open field conditions and it is easy to observe that in normal rooms the large differences that might be expected on the two sides of the head do not occur. This is no doubt due in part to the reflection of sound and to the fact that standing waves are set up. On rotating the head, or moving it a small distance when listening to a high-pitched note the noise may wax and wane, the intensity being critically dependent upon the position of the head. Such an effect may be detected at frequencies as low as 1,000 c/s. Further observations were made in a sound-proofed room at the Edinburgh University Department of Phonetics; the treatment of the walls was such that the reflection at 5 kc and over was probably slight. With one ear covered, again the loudness of the sound depended critically upon the position of the head. Evidence that the sound waves were breaking around the head to give a complex diffraction pattern was afforded by displacing the pinna. By pushing this forward with a finger it was found that the position of maxima and minima could be altered.

In these experiments it was difficult fully to evaluate the role of reflection in setting up standing waves but they did indicate that under most normal circumstances intensity cues may be more ambiguous than is sometimes supposed. Thus at times with sources fairly close to the median plane the sound was loudest in the opposite ear. On the other hand the existence of a complex diffraction pattern round the head means that small displacements of a source may be associated with larger intensity changes than might be expected.

(5) Selective Loss of Vertical Localization

There is much evidence that vertical localization depends on the integration of data as to head movements with information from the ears. Rotation of the head in the horizontal plane will give rise to little alteration in the signals from the ears if the sound source is immediately above the subject.

The twin speaker test was devised to test this mechanism. The subject

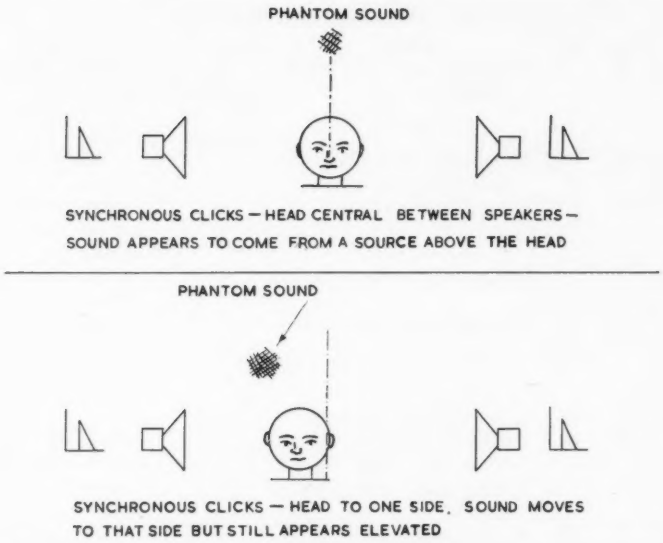
PHANTOM SOUND
SYNCHRONOUS CLICKS — HEAD CENTRAL BETWEEN SPEAKERS —
SOUND APPEARS TO COME FROM A SOURCE ABOVE THE HEAD
PHANTOM SOUND
SYNCHRONOUS CLICKS — HEAD TO ONE SIDE, SOUND MOVES
TO THAT SIDE BUT STILL APPEARS ELEVATED

FIG. 4.—*Twin speaker test.* Observer mid-way between loudspeakers pulsed synchronously hears sound as though it is coming from above.

sat midway between two loudspeakers both of which were energized at the same moment. Thus on rotating the head any change at one ear was largely offset by a corresponding change at the other. Normal people often find the illusion rather striking; the sound appears to come from the ceiling, or, if out of doors, from the sky. That the sound seems to come from above indicates the greater importance of horizontal head movements than of those in which the head is rocked from side to side about an antero-posterior axis. The results with patients suffering from the effects of neurological lesions are shown in Table VII. Three of the patients who were successful had temporal lobe lesions believed to impinge on the auditory area (C 15346, C 16651 and C 16266). A proportion of the results were anomalous, either the subject, on direct questioning, would not admit that the sound came from above or he referred to some unusual site such as the occiput.

There thus seemed need to investigate further the problem of localization in the vertical plane. A musical box movement was used for it was of small size and afforded a continuous source of sound. Clicks cannot be localized in the vertical plane unless they are repeated. None of the patients was unable to localize the sound in the horizontal plane although sometimes bias was shown towards one side, the patient regularly pointing somewhat to the right or to the left of the true

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TABLE VII.—TWIN SPEAKER TESTS

No.	*Sex*	*Age*	*Lesion*	*Results*	*Remarks*
C 15410	M	57	Vascular lesion R. hemisphere	0 (pointed to R. and below)	L. homonymous hemianopia and partial upper quadrantic defect
C 15346	F	15	R. temporal lobectomy for A-V aneurysm	+	L. homonymous hemianopia
C 16651	F	33	Cerebral atrophy	+	L. homonymous hemianopia. L. proprioceptive loss
C 16266	F	35	R. temporal lesion (vascular)	+	L. homonymous hemianopia
C 16735	F	56	Intraventricular meningioma	+	R. homonymous hemianopia, dyscalculia, dyslexia and inability to draw from memory
C 15966	F	43	L. temporal astrocytoma..	+	
C 15300	F	44	Partial L. temporal lobectomy for removal of sphenoidal ridge meningioma	0	Intellectual capacity seriously impaired. R. homonymous hemianopia
C 15873	F	64	L. temporal and occipital metatases from bronchogenic carcinoma	0	Proundly asphasic, R. homonymous hemianopia proprioceptive loss R. limbs
C 16872	M	29	L. temporal lesion (vascular)	0 (behind occiput)	Dysphasia, R. homonymous hemianopia
C 15777	M	58	L. temporal malignant astrocytoma	+	
C 15337	M	13	L. post. temporal astrocytoma	+	
C 1120	F	39	A-V malformation in region of R. Sylvian fissure	+	
C 15766	F	67	Tumour of R. Sylvian fissure reaching to insula	+	Disorientated for time
C 16217	M	39	R. fronto-temporal astrocytoma	0 (behind occiput)	
C 14831	F	36	Leucotomy..	+	
C 15888	F	40	R. frontal astrocytoma ..	+	
C 12498	F	33	R. frontal oligodendroglioma with extension through much of hemisphere	+	
C 4496	M	42	R. fronto-parietal astrocytoma	22.1.55+ 28.9.55 0 (below and behind)	Developed proprioceptive loss L. hand in the interval
C 15141	M	12	Focal epilepsy starting in L. hand	+	

C 16252	M	17	Traumatic lesion L. parietal lobe	+	Astereognosis R. hand, aphasia
C 16299	M	48	Glioblastoma deep L. parietal region	+ (above and behind)	
C 15003	M	39	Tumour L. angular gyrus..	0 (straight ahead)	Spatial orientation poor, lost way in ward, difficulties in dressing and drawing
C 10023	M	43	Bullet lodged near L. thalamus	+	Depression of proprioception and motor function R. hand
C 15880	F	45	Cyst third ventricle ..	0 ("At back of head somewhere")	Patient was lying on a trolley and somewhat drowsy
MN 1061	F	41	Brain stem lesion due to disseminated sclerosis. No deviation of eyes possible in horizontal plane	0 (to occiput)	

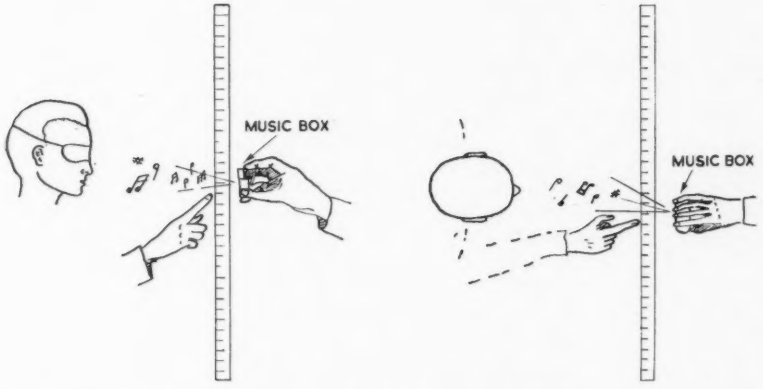

FIG. 5.—"*Diotic*" *stimulation.* Arrangements used to test ability to localize in the vertical and horizontal planes. The head was not fixed—freedom to move is essential for efficient vertical localization.

position (Table VIII). Such bias may be due to proprioceptive disturbances in the limb used for pointing, but bias may be found when this sensibility appears to be normal. Partial deafness on one side also may give rise to bias but the effects are less than might be expected—"attunement" (Greene, 1929; Meyer, 1921*a*; Jongkees and Groen, 1946).

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Labyrinthine disturbances also may introduce this type of error (Frey, 1912; Clark and Graybiel, 1949; Arnoult, 1950).

Three of the patients had probably lost the auditory cortex on one side (C 16702, C 16872 and C 15346). In two of these the performance in the horizontal plane was fair, in the other fully equal to normal. These findings are in keeping with the evidence, already presented, that such lesions leave intact certain, at least, of the neural mechanisms concerned with lateralization.

Five of the patients who succeeded with horizontal discriminations were unable to localize sounds in the vertical plane at all (Table VIII). Care was taken to use, for pointing, only limbs with unimpaired proprioceptive sensibility. Of the 5 who failed altogether three had lesions

TABLE VIII.—DIOTIC STIMULATION (fig. 5)

No.	*Sex*	*Age*	*Lesion*	*Horizontal localization*	*Vertical localization*
MN 976	F	45	Brain stem thrombosis, L. hemianæsthesia, R. facial paralysis	Normal	Impossible
C 16985	M	11	Tumour of upper brain-stem and R. post. thalamus. Vertical nystagmus and L. sided cerebellar signs	Somewhat imperfect	Impossible
MN 1061	F	41	Brain stem lesion due to disseminated sclerosis. No conjugate deviation of eyes possible in horizontal plane	Bias to R.	Impossible
C 16872	M	29	L. temporal lesion (vascular). Dysphasia, R. homonymous hemianopia	Normal	Impossible
C 16735	F	56	Intraventricular meningioma. R. homonymous hemianopia, dyscalculia, dyslexia, and inability to draw from memory	Normal	Impossible
C 16702	F	11	Traumatic lesion R. temporal lobe with L. homonymous hemianopia	Somewhat imperfect	Somewhat imperfect
C 15346	F	15	R. temporal lobectomy for A-V aneurysm L. homonymous hemianopia	Somewhat imperfect	Somewhat imperfect
C 4496	M	42	R. fronto-parietal astrocytoma ..	Normal	Normal
C 16217	M	39	R. parietal astrocytoma	Normal	Normal
C 11033	M	34	R. parietal lesion (traumatic) ..	Normal	Normal
C 16252	M	17	Traumatic lesion L. parietal lobe. Astereognosis R. hand, aphasia	Normal	Normal
C 16299	M	48	Glioblastoma deep L. parietal region	Bias to L.	Normal or poor normal

which must have been in the brain-stem. One of the three spontaneously remarked upon a disturbance of front/back relationships. With his eyes covered he repeatedly experienced the illusion that the musical box was behind him although he was fully aware that it was, in fact, in front. Fore/aft discrimination depends upon "cross-correlation" of

head movements with auditory cues, as also does localization in the vertical plane. The occurrence of this strange illusion might therefore have been predicted in patients showing evidence of a disturbance of vertical but not of horizontal discriminations.

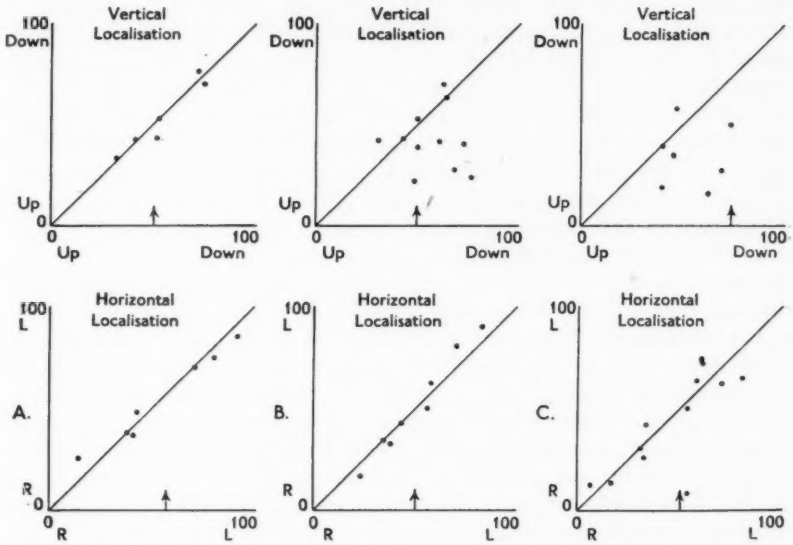

FIG. 6.—Results of diotic testing—three examples. Horizontal scales—position of musical box, vertical scales—position of hand A, Normal responses in patient with right parietal astrocytoma (but only minimal neurological abnormalities). B, Failure to localize in vertical plane. The patient was dysphasic and had a complete left-sided homonymous hemianopia caused by rupture of a middle cerebral aneurysm. C, Failure to localize in vertical plane in patient with brain-stem lesion presumed to be a thrombosis. A total left hemianæsthesia and a complete right-sided paralysis of face were found following sudden collapse. Tested twice subsequently, similar results were obtained to those shown in the figure. Even when instructed to move her head she still failed with vertical discriminations. Arrows indicate position of nose. Scales—cm., R = right, L = left.

DISCUSSION

Site, Nature and Development of Time Sensitive Mechanism

The evidence which has been presented demonstrates that as far as time differences are concerned there is nothing to support the view that a "united activity of both hemispheres" is essential for the differentiation of the direction of a sound (Pavlov, 1927). The work has shown that removal of the auditory cortex of one hemisphere does not abolish discriminations based on binaural time-differences. Although established less definitively this seems to be true also for the precedence and phase

effects. The picture that emerges is one of parallel pathways to the two hemispheres carrying duplicate copies rather than different and complementary versions of the auditory information.

In man it must be assumed that one auditory area is essential because bitemporal lesions (e.g. Mills, 1891; Bramwell, 1927) or destruction of the two auditory radiations (Le Gros Clark and Ritchie Russell, 1938) gives rise to complete deafness. It should not necessarily be assumed, however, that the messages from the two ears retain their individuality in the ascending tracts and that the time-intervals are judged by a cortical mechanism. It would seem more likely that the evaluation takes place soon after the auditory impulses from the two sides meet. If a number of synaptic junctions had to be jumped it is likely that the uncertainties of excitation would cause the short time-intervals to be lost. For these reasons special interest attaches to the recent demonstration of a nervous pathway running between the two cochleæ (Galambos, Rosenblith and Rosenzweig, 1950). It has been found indeed that the earliest neural event recordable in the auditory pathway may be modified by a preceding stimulus applied to the opposite ear. The first stimulus must precede the second by at least 1 msec. in the cat. The interval needed might well be more in man for the pathway would be several times as long. Under normal conditions, with maximal binaural time-intervals of $\frac{1}{2}$ msec., it is clear that this pathway cannot "gate" the first of the impulses to be discharged. By a process of exclusion the site of interaction between the messages from the two ears would appear to lie within the brain-stem itself.

In animals the head may be turned reflexly towards the source of a sound by mid-brain systems (Table I) but it is not certain to what extent binaural time differences are involved in these responses. It is reasonable to suggest that the binaural data are encoded at a structure such as the nucleus of the trapezoid body and that appropriate signals are sent to the cortex and to other parts of the nervous system. Jeffress (1948*a*) has suggested that the time-intervals are dealt with by the effects of latent addition at synaptic junctions and this suggestion has received some further treatment by MacKay and McCulloch (1952) who point out that "the index of latent addition falls off very sharply over a few hundredths of a millisec. when the relative delay exceeds 0·15 msec." There is clearly a need for an investigation of the electro-physiology of the auditory system in an animal with a system of sound location comparable to that of man.

The subject who had a congenital atresia of the external auditory meatus on one side is of interest for he could have had relatively little opportunity to practice binaural sound localization. He nevertheless could distinguish a sensory difference depending upon which of the ears was the first to be stimulated. Evidently the "channels" remained

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TABLE IX.—DEVELOPMENT OF ABILITY TO LOCALIZE SOUNDS

A. Human Babies

Author(s)	*First turning of eyes or head towards source of sound*	*Comments*
Darwin (quoted from Preyer 1888)	4 months (one child)	
Vierordt (quoted from Preyer 1888)	4–5 months	
Preyer (1888) ..	2½ months (one child)	Was able to localize a source *behind* him
Moore (1896) ..	1 month (one child)	*See* text. As late as 6 months could not localize sounds coming from behind
Meyer (1912) ..	2–4 months	"Wie schon öfter erwähnt, richtet das Kind in viel früheren Lebensperioden den Kopf nach einer ihm bekannten Schallquelle als nach einem ihm fremden Geräusche"
Blanton (1917) ..	13 days (one child)	
Denvies (quoted by Munn 1955)	4–39 weeks	
M. H. Draper (personal communication)	4 months 3 days (one child)	
Author	4 months 3 days (one child)	

B. Young Animals

Author(s)	*Animal*	*Age at which turning responses first appear*	*Comments*
Spalding (1873) ..	Chick	< 2 days	
Preyer (1888) ..	Guinea-pig	1 day	
Mills quoted by Cruikshank in Carmichael (1954)	Cat	9 days	
Windle (1930) ..	Cat	21 days	
Tilney and Casamajor (1924)	Cat	26 days	
Mills quoted by Cruikshank in Carmichael (1954)	Dog	21–28 days	
Lashley and Watson (1913)	Monkey (Macaca)	11 days	
Meyer (1921*b*) ..	Jaguar	⩽ 5 months	These animals appear to have been tested once only at the ages given. Sound localization may have become established long before test
	Elephant	⩽ 5 months	
	Leopard	⩽13 months	

open even though largely unused for twenty years though it is often assumed that in man sound localization is dependent upon learning.

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Spalding (1873) wrote that: "perceptions of auditory space in man at least, even Mr. Spencer regards as acquired by each individual." Infants start in response to sounds some weeks before they will turn to the appropriate side (Table IXA). This delay does not appear to be due to a lack of myelin on the sensory side for Keene and Hewer (1931) found that the human auditory system was myelinated by 28 weeks of fœtal life.* In the cat the auditory pathways are myelinated at birth (Tilney and Casamajor, 1924) and in this animal, too, localization cannot be demonstrated until a later date (Table IXB).

It must not be supposed that all of the sound location mechanisms become functional simultaneously. Moore (1896) has noted that lateralization precedes the ability to make fore/aft discriminations. She wrote of the development of her own child that "By the eighteenth week he could locate very well sounds coming from objects within the visual field. . . . In the twenty-seventh week, when he could sit, it was found that he could not localize sounds that came from behind him, but looked for their sources in front." The young chimpanzee, too, may have difficulty with front/back discriminations (Kellogg and Kellogg, 1933). The integration of sensory data concerning head movement with that from the ears evidently depends upon a system that takes time to mature, or depends on learning. It is presumably this same set of nervous connexions that is damaged in those patients who have a selective loss of localization in the vertical plane.

Summary

Sound localization has been studied in patients with neurological lesions.

The sensitivity to binaural time differences is retained after the loss of the auditory cortex on one side.

The ability to localize sounds in a vertical plane may be lost whilst localization in a horizontal direction remains possible.

* * * * *

The author wishes to acknowledge the encouragement of Professor D. Whitteridge and to thank those physicians and surgeons who facilitated this work. Hospital numbers prefixed by the letter C refer to patients, treated in Ward 20 of the Royal Infirmary, Edinburgh, who were under the care of Professor N. M. Dott.

*Up to the level of the medial geniculate body. According to Flechsig (*Gehirn and Seele*, 1896) the auditory radiations are incompletely myelinated one month after birth.

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THE CONDITIONED INHIBITION OF UNCINATE FITS

BY

ROBERT EFRON

Department of Neuropsychiatry,[1] *U.S. Naval Hospital, St. Albans, N.Y.*

I. Historical Background

It has been repeatedly observed, since ancient times, that a specific sensory stimulus could arrest epileptic fits, but the physiological explanation of this phenomenon is still unknown.

Similarly, seizures spontaneously arrested during the aura (aborted for reasons which cannot be ascertained, but not *apparently* by sensory stimulation) are reported by almost every epileptic from time to time. In one of the rare references to this phenomenon in the last twenty years. S. A. K. Wilson (1935) noted that the grand mal fit sometimes "fails to evolve according to rule . . . the process becomes arrested at some point, for reasons difficult to fathom." He called these abortive fits "fragments."

It has also been observed that spontaneous arrests during different stages of the aura are more frequently noted after treatment with anti-convulsant drugs, especially phenytoin. (The suggestion so often made when a spontaneous arrest or "fragmentary" fit occurs—that the "threshold for the spread of the fit was not achieved at that moment" is mere tautology.)

This phenomenon of seizure-arrest, known for so long, has not been seriously investigated in the laboratory or clinic although hundreds of papers have recently been published on methods of precipitating fits. This neglect is surprising since a study of naturally arrested seizures is both of theoretical interest and pertinent to therapy.

In the last and most exhaustive study of the phenomenon of sensory arrest of seizures, Gowers (1881) pointed out that the repeated arrest of Jacksonian fits by ligatures could permanently alter the subsequent development of the fit. He reported the case of a "patient whose fits always commence in the hand by a sensation which passes up the arm, and could be arrested by the ligature applied just above the elbow. After employing the ligature in this manner for some months, he found that the fits, commencing in the same way, stopped of their own accord at the spot

[1]The opinions expressed in this article are those of the author and are not necessarily to be construed as representing those of the Navy Department or the Naval service at large.

Present address: Neurological Research Unit, National Hospital, Queen Square, London.

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at which they had been repeatedly arrested by the ligature. They never stopped thus before the patient commenced the use of the ligature, which appeared to have produced a permanent increase of resistance at a certain part of the unstable nerve tissue."

Another case of permanent cure by application of the ligature, reported originally by Lysons (1772) was mentioned by Gowers. In Lysons' patient, the fits began in the foot and were arrested by repeated applications of a tight garter at the knee at the onset of each fit. "The fits afterwards became weaker, and the same means being used, whenever notice was given of their approach, they were at last entirely cured without medicine."

Lysons did not indicate, however, whether or not his patient continued to experience the early phases of the fit. Gowers' patient continued to have fits which were spontaneously arrested without any *apparent* sensory stimulus from a ligature.

II. Present Investigation

In reading these case reports one is forcibly struck by the resemblance of this phenomenon to the establishment of conditioned reflexes in animals and man by the repeated temporal association of a non-specific (conditioned) stimulus with a specific (unconditioned) stimulus. Indeed, Gowers' own language—"permanent increase of resistance . . . of the unstable nerve tissue"—is almost identical to that used by I. Pavlov (1928) in explaining the behaviour of his dogs. To use this analogy: we may say that the ligatures (specific unconditioned stimuli) became linked, as a result of repeated temporal association, with a non-specific stimulus—which in turn became as effective in arresting the fit as was the original "specific" ligature itself. We cannot determine, from the reports of Gowers and Lysons, what the non-specific stimulus might have been in their patients.

In a previous paper by the author (1956) a case of temporal lobe epilepsy was reported which was characterized by depersonalization, forced thinking, olfactory hallucination, auditory hallucination and adversive head movement preceding the *grand mal* climax. These attacks had persisted for twenty-six years and the sequence had been identical for each fit. No arrested seizures had ever occurred: once the first part of the aura had begun, a stereotyped fit was inevitable. Application of a specific sensory stimulus (an unpleasant odour) prior to the stage of forced thinking, invariably arrested further development of the aura and prevented the occurrence of the tonic and clonic seizure. Application of the unpleasant odour at the appearance of the stage of forced thinking, resulted in bizarre fragments of adversive seizures, gyratory epilepsy and epilepsia cursiva. Further delay in administration of the stimulus failed to alter the pattern of the seizure in any way.

The patient has since been able to arrest every seizure by inhaling from

a vial the odours of various aromatic chemicals or essential perfume oils. The frequency of her attacks has remained unchanged. The only failures to arrest seizures have been at night when she slept throughout the early phases of the aura (which on other occasions had awakened her) and had no opportunity to inhale the essence. For details concerning the lysis of the aura as a result of these stimuli, the reader is referred to the original report.

In attempting to explain, in physiological terms, the effectiveness of the olfactory stimulus in our patient, the activation of a widespread inhibitory system by the unpleasant (nociceptive) olfactory stimulus was predicated. It was assumed that the nociceptive stimulus activated this inhibitory system in a "reflex" or automatic fashion. Yet, Gowers' patient was eventually able to inhibit his fit *without* the application of a nociceptive stimulus. It thus seemed possible to produce an activation of this reflex fit inhibition (originally produced by a nociceptive stimulus) by a conditioned, non-specific stimulus, in the same way that a dog may eventually be led to salivate by hearing a tuning fork.

It is the object of this paper to report the arrest of seizures not only by a conditioned, non-specific visual stimulus but also by a second order conditioned reflex (2° C.R.) which was concurrently, but inadvertently, established.

III. Methods

Every fifteen minutes (approximately) for a period of eight days, two stimuli were simultaneously presented to the subject. The first was a concentrated odour of jasmine which had previously been found effective in arresting the uncinate seizures. The second was an inexpensive silvered bracelet. She was instructed to stare intently for 15–30 seconds at the bracelet while sniffing a vial of essence of jasmine.

The patient was permitted seven hours sleep at night and the conditioning was begun anew each morning lasting until bedtime. Five different persons[1] exposed her to the sight of the bracelet and to the jasmine odour during the eight-day period, so that the response would not depend on the presence of any particular person. Similarly, the double stimulation was performed in the patient's hospital room, the day room, during walks in the hospital grounds, and while reading, etc., to avoid unrelated conditioning by specific aspects of her environment. Except for the 15–30 second interval during which the stimuli were simultaneously applied, the subject was not exposed to either of them.

Twice during the eight-day conditioning period the patient developed spontaneous seizures, each of which was arrested by the use of the odour alone. This unintentional failure to reinforce the conditioning process

[1]T/Sgt. R. Koran, U.S. Air Force; T/Sgt. C. Martin, U.S. Army; HM2 M. Cassidy, U.S. Navy; HM3 M. Shepherd, U.S. Navy; HN J. Cohill, U.S. Navy.

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occurred because the attacks developed at night after the bracelet had been removed from her room.

IV. Interpretation of Results

At the end of eight days of conditioning the bracelet alone was presented to the patient and she experienced the odour of the concentrated jasmine in a vivid fashion. The olfactory hallucination persisted while the bracelet was exposed and receded in a few seconds when it was removed from her sight.[1]

For the next week the patient was exposed only twice a day . . . to the bracelet and the jasmine, a programme instituted to maintain reinforcement. During the second week *a spontaneous seizure occurred which was arrested by the patient's merely staring at the bracelet for a few seconds.*

This seizure began in its stereotyped form and the patient reported its arrest as a gradual lessening of the intensity of the depersonalization, remoteness and dreamy state. There were two significant subjective differences, however, in the response to the specific stimulus (essence of jasmine) and the one to the non-specific conditioned stimulus (bracelet). The patient reported that the "dissolving" of the seizure began later after exposure to the bracelet, than it usually did after exposure to the essence of jasmine. This increased latency of response is a finding usually noted in conditioned reflexes as compared to unconditioned reflexes. In addition, she described the lysis itself as more "abrupt" when terminated by the essence of jasmine. When the bracelet was used, the fit "faded away" more slowly, and this appeared to be a consistent finding in further arrests with the bracelet. As the lysis of the depersonalization was gradual in both cases and persisted for about "half a minute," it was difficult to be certain of the precise moment the lysis began and the exact moment normality was achieved. For this reason, measurements of the latency and the duration of the lysis were impossible to obtain with any accuracy.

Following this success, the patient was permitted to go home with only the bracelet to control her seizures. (Anticonvulsant medication had been discontinued after the initial success with aromatic chemicals some months previously.) The patient entirely discontinued the use of the vials of aromatic chemicals, and successfully used the bracelet to arrest seizures for a period of eight months. Further formal reinforcing conditioning has not proved necessary, as each arrested seizure appears to serve as a reinforcement.

On three occasions, shortly after the initial success with the bracelet,

[1]This type of response to conditioning is not unusual. The work of C. and N. A. Popov of Paris (1953, 1954, 1955) showed that visual hallucinations (after-images) can be easily induced by Pavlovian techniques. Further reference will be made to their work in the discussion.

the patient was instructed to delay the exposure of the bracelet until later in the aura (just prior to the olfactory hallucination) to see if any forms of larval epilepsia cursiva or gyratory epilepsy would develop—as they had when applications of the primary olfactory stimulus was delayed. In the first two of these attempts, the patient experienced such passivity and inertia at this late stage of the seizure, that she was unable to get up to take the bracelet out of her purse. She experienced a complete *grand mal* seizure both times.

On the third occasion, at the earliest stage of the aura, she removed the bracelet from her purse (without looking at it), and placed it on a table in front of a chair. Then, with head averted, and eyes open, she sat in front of it, having only to turn her head to bring the bracelet into view. The patient reported that in performing these activities she was extremely conscious of the existence of the bracelet at all times, and was puzzled as to the slowness with which the aura developed in this particular fit. However, she finally reached the stage of forced thinking, impending olfactory hallucination, and passivity, when she turned her head and looked at the bracelet. She experienced the smell of jasmine and the fit rapidly subsided without the development of the *grand mal* component. This was the first time that success had been achieved at such a late phase in the fit.

Following this, no further delays were suggested and the patient continued, *without fail*, to arrest seizures by staring at the bracelet in the early phase of her attacks. She had attacks at about the same frequency as before. With continued practice, she became more socially adept at controlling her fits in varying situations. On one occasion, while performing at a theatrical benefit, she was forced to leave her purse in a distant room. Fearing the possibility of a seizure while performing before a large audience, she put the bracelet on her wrist, and covered it with a kerchief. During her song, she began to experience the characteristic depersonalization of her attacks. She also noted that the conductor was signalling for her to slow down. (Her disturbed time sense in an early stage of the aura has been previously reported.) She uncovered her bracelet while singing. The hallucination of jasmine and the lysis of the aura occurred, and she finished her performance uneventfully. Only the conductor knew that "something had gone wrong".

V. Electroencephalographic Studies

In the previous investigations of this patient, EEG confirmation of an arrested seizure (aborted by B.A.L.) was obtained with the aid of metrazol activation. On one occasion 75 mg. metrazol induced a self-sustained seizure and on another 50 mg. did so. A third attempt was made to perform the experiment using the bracelet as the arresting stimulus. Sphenoidal electrodes were placed by a modification of the techniques of

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Arellano and MacLean (1949) and adequate control tracings were secured. Metrazol was administered intravenously in the dosage of 30 mg. over a two second period every thirty seconds. Once the aura was precipitated the metrazol infusion was discontinued. The whole procedure was similar to prior procedures, including the placing of the sphenoidal electrodes with local cocaine anæsthesia. The single difference was that where, in the earlier experiments, the patient was told that the vial of aromatic chemical would be placed beneath her nostrils at the critical moment—on this occasion she was instructed to open her eyes at the critical moment in order to see the bracelet about two feet away.

Two very surprising things happened. In the first place, injection of 60–90 mg. metrazol failed to precipitate even the earliest stages of the patient's specific aura. It was found that rapid injection of 150 mg. was necessary to "switch" from the fright and lightheadedness that normally follows a metrazol injection, to the patient's own characteristic type of depersonalization, dreamy state, etc. . . . the hallmarks of her fit. Secondly, the fit did not progress as it had on previous occasions. Even though the bracelet had not yet been viewed, the patient reported that the aura was "hung up," meaning by this that the subjective intensity was not worsening, that the depersonalization and dreamy state were static. After being "hung up" in such a fashion for about two to three minutes she reported that the fit was subsiding. After she experienced, for the first time in her life, four such *spontaneously* abortive attacks, it was realized that the threshold for metrazol had changed in two respects. Firstly, more was required to precipitate an attack. Secondly, the aura, once precipitated, did not sustain itself and progress into a full-blown fit. Because of this resistance to metrazol, an attempt was made to sustain the aura, and cause it to progress by continuous infusion of metrazol.

After a five-minute rest period, the patient was given 150 mg. metrazol over a one-minute period and 50 mg. every 30 seconds thereafter. She reported the onset of a fit, in the usual fashion, and even at this rate of continued metrazol infusion the aura remained almost motionless, with perhaps the slightest progression, for ten minutes. She received a total of 1,150 mg. over this eleven-minute period. Opening her eyes and viewing the bracelet resulted in a rapid lysis of the subjective sensations of the fit *despite* the fact that metrazol was still being slowly infused. The patient was made extremely anxious by this procedure, and in view of the large quantities of metrazol administered (1,350 mg. in thirteen minutes), the procedure was discontinued.

Although five different fits were induced, only the earliest psychic stages could be precipitated, there being an obvious resistance offered by some mechanism to the development of a self-sustaining fit. The EEGs showed no localized or generalized abnormality during the stage of the aura. When the patient was reporting the lysis of a seizure, either by

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use of the bracelet or spontaneously, some bursts of high voltage 30 cps activity were recorded from the bisphenoidal electrodes.

VI. Development of a Second Order (2° C.R.) Conditioned Reflex

On questioning the patient subsequently about her reactions during the metrazol infusions, it emerged that she was thinking almost continuously about the bracelet, whether it would really be presented to her in "time," and whether it would "work," etc.

It seemed plausible that the alteration in the patient's sensitivity to metrazol was caused by a *premature activation* of the "inhibitory" mechanism—precipitated by *thinking* about the bracelet. This might serve not only as an explanation for the results of the experiment with metrazol but for the earlier success of the bracelet in the late stage of the aura just prior to the olfactory hallucination.

It thus became essential to prove that the patient's seizures could be arrested by having her think of the bracelet when a spontaneous fit developed. The test was made and *the act of thinking intently about the bracelet proved sufficient to inhibit the seizure.* When the patient merely thought of the bracelet she also developed the olfactory hallucination of jasmine.

The patient reported that it took even longer for the fit to begin to subside when she was thinking of the bracelet than it did when she actually looked at it. She was not certain that there was any change in the time taken to return to normality.

For a period of six weeks the patient continued to arrest her seizures by thinking of the bracelet as the seizure developed. During this period, she observed that on several occasions, when she did *not* think of the bracelet, a spontaneous odour of jasmine suddenly enveloped her. This occurred once at night during this early period and awoke her from sleep. However, at these times she had no subjective manifestations of her seizure.

The spontaneous hallucinations of jasmine, lasting for one to one and a half minutes became increasingly frequent over the next three weeks, during which time she experienced fewer seizures. Those seizures which did develop were arrested by thinking of the bracelet. For *fourteen* full months, the patient has had no seizures at all. She developed no episodes of depersonalization and did not need to rely upon any external method of arresting attacks: she experienced only spontaneous, abrupt (one minute) hallucinations of smell. At these times, she did not "smell" the original odour which was associated with her uncinate discharges, but, instead, was "overwhelmed" by the odour of jasmine.

For the first four to six months these hallucinations occurred at the same frequency (seven to fifteen a month) as did her original uncinate seizures. This six-month period of frequent olfactory hallucinations

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(but no seizures of any type) was followed by another eight-month period during which she was still free of seizures, but had only three episodes of hallucination. Two of these were at night and awakened her, the third occurred while she was singing.

Although she was at first extremely anxious and preoccupied about her experiences, she soon adjusted to her hallucinations of jasmine, and now that she has no seizures or hallucinations she has returned to a full-time singing career. She considers herself "cured" as she had not, in the previous twenty-six years, been free of seizures for more than a fortnight.

VII. Discussion

In our attempt to "explain" the case reports of Gowers and Lysons, it had been assumed that a conditioned reflex had been established in their patients which then served to arrest the focal seizures as the ligatures had done previously. In this patient, a conditioned stimulus (bracelet) arrested uncinate seizures just as successfully as did the primary unpleasant olfactory stimulus. Furthermore, the thought of the bracelet was later sufficient to arrest a seizure.

Hudgins (1933) has shown that the pupillary reflex in man could be conditioned to the sound of a bell, and that a second order conditioned response could then be established between the bell and the spoken verbal command, "constrict." Finally, the spoken command was conditioned, by frequent repetition to the thought "constrict." Upon completion of this complex series of conditioning experiments, Hudgins' subjects could constrict their pupils by merely thinking the word "constrict." The latency of the response was about seven to ten times longer than the latency of the direct pupillary response to light.

Similarly, Jasper and Shagass (1941*a* and *b*), Shagass (1942, 1943) Laufberger (1950), as well as Travis and Egan (1938) conditioned the alpha blocking reaction in the human EEG to a sound. Following Hudgins, they then conditioned the blocking response to the verbal command "block" and finally to the thought "block." Laufberger (1950) conditioned the alpha blocking response to a phoneme and showed that the thought of the phoneme would similarly block the alpha rhythm. In these experiments the investigators were conditioning an electrical response of the cortex to stimuli which were ineffective in altering the EEG pattern prior to the conditioning procedure. Jasper and Shagass (1941*b*) described in detail how every type of conditioned reflex in dogs, as described by Pavlov, could be similarly established in the human EEG by using the alpha blocking response as the test indicator. They were able to produce simple conditioned reflexes, delayed, differential, differential delayed, and cyclical conditioned reflexes. They also showed tracings which clearly depicted "anticipation" of the conditioned blocking response in cyclicial conditioning. There seems to be little difference

between "anticipation" as seen in Jasper and Shagass' records and the "premature activation of the inhibitory mechanism" which we have just postulated.

Morrell and Jasper (1956) have gone even farther and have convincingly demonstrated in monkeys that not only alpha-blocking responses could be conditioned, but that certain occipital augmentation rhythms (photically activated) could be conditioned in identical fashion. They found that a photic flicker rate of eight cycles per second produced a frequency-specific occipital response, and that this cortical response could be produced by the conditioned stimulus after a suitable number of paired stimuli. Similarly, a cortical response to a twelve cycle per second flash could be conditioned to a 500 cycle per second tone and the frequency of the cortical response to that tone was at 12 cycles per second. Sounding a 1,000 cycle per second tone would not evoke any occipital augmentation pattern.

The work of the Popovs is also most interesting. They, too, have conditioned the alpha-blocking response to a sound stimulus, but they have been primarily studying after-images. They have found that at the time when the alpha rhythm blocks to the specific conditioning sound stimulus, the subject reports seeing after-images—identical to those after-images experienced following the original light flash. They have thus claimed that the after-image is not primarily a retinal reaction, such as might be due to regeneration of visual purple, but, rather a purely cerebral response as it can be produced without light by a conditioned reflex.

These experiments in human beings (Hudgins, Shagass, Jasper, the Popovs, Travis and Egan, Laufberger, etc.) and in lower animals (Jasper, Morell and Jasper, Morrell and Ross, the Popovs) in which *normal* neurophysiological responses have been conditioned to an indifferent stimulus, and finally (in man) to the thought of the indifferent stimulus, closely parallel our attempt similarly to condition a *pathological* response of neural tissue—a fit.

That pathological neural responses (fits) *can* be conditioned has been known for many years. James Dunsmure (1874) presented a case of a boy whose fits could be readily elicited by patting him on the head. However, if he was prepared for the stimulus, a fit did not occur. Jackson (1887) similarly described a patient whose fits were always precipitated if his face were touched, especially if there was an element of surprise in the touch. If he thought that his face would be touched, the stimulus would not evoke the fit. In this case, the reflex epilepsy could be inhibited. Wilson (1930) described another such case.

In recent years, Mitchell, Falconer and Hill (1954) reported the case of a fetishist with temporal lobe epilepsy who would precipitate fits (auto-erotically) by staring at a safety-pin. He found that scissors and paper clips were also effective, but less satisfying methods of producing his fits.

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Following temporal lobectomy which cured him of both fits and fetish, he told how, previous to surgery, merely "phantasizing" a safety-pin in his mind was an adequate stimulus to produce an attack. In this case, the displacement from the specific stimulus to the intellectual or symbolic conception of it, was still sufficient to "trigger" the mechanism.

We now find an analogy in our patient who was eventually "cured" of her seizures by repeated arrests by sensory stimuli or by their conditioned equivalents. Review of the literature does not reveal a similar case although it is strongly suspected that Gowers' (1881) case may have been due to an identical mechanism. Similarly, the "cure" of focal seizures by repeated application of the ligature which Lysons (1772) described is probably explicable on this basis.

In the case of our patient, the spontaneous hallucinations of jasmine which occurred for six months at the same frequency as did the original seizures, and then disappeared, probably represents an extreme degree of "anticipation" . . . that is, the inhibitory mechanism, once conditioned, is now being activated almost immediately after the initial epileptic discharge commences. With the activation of the reflex fit inhibitory mechanism occurring prior to the development of any *subjective manifestations* of the fit, the patient experiences only the manifestations of the inhibitory reflex (hallucination of jasmine). She would most likely be unaware that a fit had started and might have matured, had this hallucination not occurred. It is not clear, at the present time, why even the hallucinations of jasmine have disappeared. It may represent even a further degree of anticipation, or may possibly reflect a decay in the conditioned reflex as a result of lack of reinforcement.

Recalling S. A. K. Wilson's (1935) remarks about the high frequency of fragmentary seizures in all epileptics, we may wonder if these, too, are not examples of fit inhibition, either by an undetected sensory stimulus, or perhaps by an intellectual event. It is not infrequent to hear a patient describe twice as many auræ as fits and to have him claim that he "fights off" half of his attacks. Such methods of arresting seizures in other of our patients currently under treatment are: "intense concentration on the conversation or on the radio," "rapidly putting my head between my knees," "getting up to walk it off," and "eating a piece of chocolate" (sugar is not effective). In a child of 6 years, his mother has found that his focal, adversive attacks which are followed by complete immobility can be arrested by tickling him at the onset of the adversive movement. Sometimes his fits stop when he sees his mother approach to tickle him. The family of a 19-year-old boy has discovered that a quick jerk of his head in a direction opposite to the first adversive movement will abort a *grand mal* seizure.

Reflex fit precipitation (musicogenic, photogenic, etc.) has been studied extensively, as it has been thought by some to be frequent if specifically

looked for, whereas reflex fit inhibition has been almost totally neglected in recent times as it is considered to be extremely rare. Yet we may be fairly certain that the mechanism of one is closely related to the other. They must both represent converse aspects of the process of excitability of neural tissue. This would seem to be a fruitful area for therapeutically oriented research.

SUMMARY

(1) A patient who had been able to arrest uncinate seizures by a properly timed, unpleasant olfactory stimulus was conditioned (Pavlov) to a non-specific visual stimulus. After conditioning, seizures were as successfully arrested by the visual stimulus as they had previously been by the olfactory stimulus.

(2) It was discovered that the "intellectual" act of thinking about the visual stimulus was equally effective in arresting seizures.

(3) Metrazol activation studies following conditioning showed a marked decrease in sensitivity to this drug.

(4) The clinical literature referable to conditioned inhibition and conditioned precipitation of seizures is reviewed and the physiological studies of electroencephalographic conditioning are described.

(5) An analysis of the physiological mechanisms is attempted.

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OBSERVATIONS ON THE TOPOGRAPHY OF THE LATERAL COLUMN OF THE HUMAN CERVICAL SPINAL CORD

BY

MARION C. SMITH[1]

IT is customary to picture the location of the long tracts of the spinal cord as being fairly constant throughout the whole length of the cord. Therefore, when considering which tracts are likely to be involved in a lesion, a single diagrammatic conception of tract distribution is usually applied, regardless of the cranio-caudal site of the lesion. But the fibre pattern is in fact much more complicated, some of the tracts shifting in location from segment to segment. Moreover, in some instances the fibres of one tract have been erroneously attributed to another tract, as this shifting location of tracts has not been noticed. These changes in fibre pattern are particularly marked in the cervical cord; in this region there are considerable differences even in different levels of the same segment.

The purpose of this paper is to describe the changing relations of the largest groups of fibres in the lateral column of the cervical cord. These relations have been established from a study of 100 cases of tract degeneration in man.

MATERIAL AND METHODS

In the course of a clinico-anatomical study of patients who have had various pain relieving operations on the lateral column of the cervical cord the central nervous system from 55 patients has been examined histologically. This material is particularly suitable for determining the precise anatomy of certain tracts which have been cut at operation, as these tracts degenerate and therefore can be clearly demonstrated histologically. In addition, the cords of patients who have had various pathological or accidental lesions of the cord or of the brain, resulting in degeneration of certain tracts, have also been studied. The cords of human fœtuses of different ages, and the cords from neurologically normal adult patients have also been used.

In the majority of the cases every segment of the cord has been examined histologically, a variety of stains has been applied to confirm the findings.

[1]From the Neurological Unit of the Medical Research Council, National Hospital, Queen Square, London, W.C.1

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Observations

The arrangement of the large groups of fibres in the lateral column of the human cervical cord will be considered in the following order: first, the changing pattern of the ascending fibres; second, certain features of the pattern of the descending fibres associated with the changes in the ascending fibre pattern; third, the changing relation of the posterior and anterior spino-cerebellar fibres to each other; and fourth, the relation of the spino-thalamic and associated fibres to the spino-cerebellar fibres.

In describing the location of tracts in the lateral column, the cord is arbitrarily divided coronally by an imaginary plane which passes through the central canal; the part of the column lying between the posterior horn and this plane is described as posterior, and the part lying anterior to this plane as anterior. The groups of fibres are described in accordance with their appearance in transverse sections, and the region where the coronal plane transects the periphery of the cord is referred to as the level of the central canal.

In most of the figures the sections are Marchi preparations, in which degenerating fibres are stained black.

First, the changing pattern of ascending fibres.—Fig. 1 (Plate XXIV) illustrates the course of the ascending fibres of the lateral column, entering the cervical cord from the thoracic cord. In this case there was a transverse lesion of the cord at the third thoracic segment, and there is degeneration throughout the ascending lateral column fibres (fig. 1, T_3). In the lower cervical region the degenerating fibres form two main groups, a posterior group consisting of posterior spino-cerebellar fibres, and an anterior group consisting of anterior spino-cerebellar fibres, together with spino-thalamic and associated fibres (fig. 1, C_7). The posterior group is narrower than the whole anterior group; the posterior group is broader in the posterior than in the anterior part. This arrangement of the fibres remains fairly constant between the eighth and fifth cervical segments. But in the fourth cervical segment the distribution of the degenerating fibres is altered (fig. 1, C_4). Here the fibres are more closely packed, extending less far in a postero-anterior, and further in a medial direction. There is at this level an area of non-degenerating fibres on the periphery, separating the mass of degenerating fibres from the posterior horn. In the third cervical segment the arrangement of the fibres is similar, but in the cranial part of the second segment and in the first segment the mass of fibres has become somewhat narrower, and some of the degenerating fibres are again in juxtaposition with the posterior horn (fig. 1, C_1). It may be noted that the posterior limit of the degenerated fibres has not shifted so far posteriorly as might appear, for the shape and position of the posterior horn has altered so that it is larger, and extends further anterior in the first cranial segment.

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It has therefore been shown that the pattern of ascending fibres in the lateral column of the cervical cord varies in different segments. In the eighth to the fifth segments the fibres form a band from the posterior horn along the periphery, but in the fourth and third segments the fibres form a more compact mass, and none of them lies in juxtaposition with the posterior horn. In the second and first cervical segments the fibres are in a band along the periphery and some of them lie in contact with the posterior horn.

Second, certain features of the pattern of the descending fibres associated with the changes in the ascending fibre pattern.—Fig. 2 is from a case in which there was degeneration of the cortico-spinal fibres due to an internal carotid artery thrombosis. The cortico-spinal fibres are shown by the lack of staining. In the medulla (fig. 2, M) there is pallor of the right pyramid; in the cranial part of the second cervical segment (fig. 2, C_2) the left lateral cortico-spinal fibres lie in the medial position where one usually pictures them, but in the third cervical segment (fig. 2, C_3), some of the degenerated cortico-spinal fibres lie on the periphery of the cord, immediately anterior to the posterior horn.

The next figure (fig. 3) shows sections from a 26-week-old fœtus, in which the cortico-spinal fibres are not yet myelinated, and are therefore unstained. Here the area of unstained fibres can be seen on the periphery in the fourth cervical segment (fig. 3, C_4) but by the fifth cervical segment (fig. 3, C_5) it lies deep to the myelinated spino-cerebellar fibres.

It has already been shown that at the third and fourth cervical segments the spino-cerebellar fibres do not occupy the most posterior part of the postero-lateral column. It is now obvious from the last two cases that this region is occupied by cortico-spinal fibres.

The next feature which will be demonstrated is that in the lower cervical segments the lateral cortico-spinal fibres again approach closer to the surface, at a more anterior level. This is evident in the fifth cervical segment (fig. 3, C_5) of the fœtal cord. In the next case (fig. 4) there was a cordotomy lesion affecting descending fibres in the third cervical segment (fig. 4, C_3). In the lower cervical segments (fig. 4, C_5) degenerating descending fibres may be seen to lie close to the surface. Compare this with the arrangement of the ascending fibres in the lower cervical segments shown in the next case (fig. 5, C_5) in which there was a cordotomy lesion in the fifth thoracic segment (fig. 5, T_5). It can be seen that there are fewer spino-cerebellar fibres about the junction of the middle and anterior thirds of the postero-lateral zone than at other parts of the periphery of the lateral column. This is the same region where descending fibres approach the surface. From the ascending fibre pattern at the lower cervical level one gains an impression that this zone (X) indicates a division of the fibres into two groups, a posterior and an anterior. This impression has led some workers to divide the spino-cerebellar tracts

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into two at this zone, those fibres posterior to X being called posterior (or dorsal) spino-cerebellar, and those anterior to X being called anterior (or ventral) spino-cerebellar. But this is not an accurate point of separation of the fibres into two groups, for in the thoracic and in the lower cervical cord the separation between the posterior and the anterior bundles lies further anterior than this zone, at about the level of the central canal. This will be discussed in the next paragraph.

Third, the changing relation of the posterior and anterior spino-cerebellar fibres to each other.—In the lower cervical cord two distinct groups of ascending fibres on the periphery can be identified, one in the postero-lateral and the other in the antero-lateral region. As said before, the separation between these two groups lies approximately about the level of the central canal, for a lesion of fibres anterior to this level (fig. 6, T_5) results in ascending degeneration confined to the antero-lateral column (fig. 6, C_5) whereas a lesion affecting also the lateral column fibres just posterior to this level (fig. 7, T_9) results in ascending degeneration in the postero-lateral column, some of the fibres in this column gradually shifting posteriorly during their ascent to lie close to the posterior horn (fig. 7, C_5). There is then in the lower cervical cord a definite grouping of the peripheral spino-cerebellar fibres into two separate bundles. The posterior bundle extends from the posterior horn to about the level of the central canal, and the anterior bundle from this level to about the level of the most lateral anterior nerve roots. We will now follow each of these two bundles through the cervical cord. Figs. 8 and 9 are from two comparable cases, in one only the posterior group of lateral column fibres is involved in the left cordotomy lesion (fig. 8, T_5), and in the other only the anterior group (fig. 9, T_5). In fig. 8 the degenerating fibres can be seen in the fifth cervical segment (fig. 8, C_5) to occupy the posterior part of the peripheral field, and in the third cervical segment (fig. 8, C_3) they can be seen to shift anteriorly, as already noted. Then, in the upper cervical segments (fig. 8, C_1) they move posteriorly again to lie in juxtaposition with the posterior horn. The posterior shifting of some fibres of the postero-lateral group during their ascent can be seen on the right side. In the other case (fig. 9) where the left lesion involves only the anterior quadrant (fig. 9, T_5), in segments cranial to the lesion (fig. 9, C_5) up to the third cervical segment (fig. 9, C_3), the degeneration is confined, on this side, to the anterior quadrant. But in the first cervical segment (fig. 9, C_1) these fibres have moved posteriorly to occupy the same region as is occupied in fig. 8, C_1 by fibres of the postero-lateral column. It is obvious that many of the fibres of the anterior group must intermingle completely with those of the posterior group in the cranial two cervical segments. This is shown also in the next case (fig. 10). Here the lesion on each side did not involve more than a few posterior fibres (fig. 10, C_5 and $_6$). But in the upper cervical segments many of the fibres lie in the

postero-lateral zone (fig. 10, C_1 and $_2$). It is clear that in the first and second cervical segments the identity of the anterior spino-cerebellar group is almost entirely lost, and that a new group of spino-cerebellar fibres consisting of both so-called posterior and anterior fibres is formed. Thus we see that the fibres of the posterior spino-cerebellar tract and those of the anterior spino-cerebellar tract pursue separate courses in the spinal cord until they reach the fourth and third cervical segments. In this region the two tracts become more closely merged, and in the second and first segments many anterior, as well as posterior, spino-cerebellar fibres move posteriorly and the two tracts, posterior and anterior spino-cerebellar, are almost completely intermingled.

Fourth, the relation of the spino-thalamic and associated fibres to the spino-cerebellar fibres.—As many of the fibres of these systems are fine, they are not so easy to demonstrate in degeneration studies as are fibres of coarser calibre, and this is particularly so when the survival is long. Therefore it is more difficult to show in any one case all one would like.

In the case shown in fig. 10 some ascending fibres can be seen to lie medial to, and extend farther anterior than, the main mass of fibres. In the next case (fig. 11) the lesion was made in the third cervical segment (fig. 11, C_3). In segments cranial to the lesion medial lying fibres can be seen extending as far anterior as the limit of the lesion (fig. 11, C_1). The peripheral fibres do not extend so far anterior. And in the last case (fig. 12), in which the lesion involved the whole anterior quadrant (fig. 12, C_1-$_2$), medial lying fibres can be seen extending almost to the anterior fissure (figs. 12, C_1 and M-C_1). In this case the medial group of fibres can be seen to be distinct from the peripheral group, which has moved posteriorly at this level, so that only the most anterior fibres have been cut and are degenerating.

These fibres which form the medial group are mostly spino-thalamic, spino-reticular and associated fibres. They extend much farther anteriorly than the more peripheral spino-cerebellar group, and they do not shift so far posteriorly in the upper cervical segments into the most posterior zone as do the spino-cerebellar fibres.

The observations which have been briefly discussed here are summarized in fig. 13. It must be stressed that these diagrams give only a crude indication of the fibre pattern, for it is erroneous to picture the fibres of any one system as forming a very definite fasciculus in the spinal cord. There is considerable overlapping of the fibres of different systems, with a predominance of fibres of each system in certain distributions. Also, individual fibres in a system alter their relationship to each other from segment to segment. Diagrams such as those in fig. 13 are useful only in indicating the location of the main mass of fibres of a tract.

It has been shown above that there is a considerable alteration in the relations of the long tracts of the lateral column of the cervical cord to

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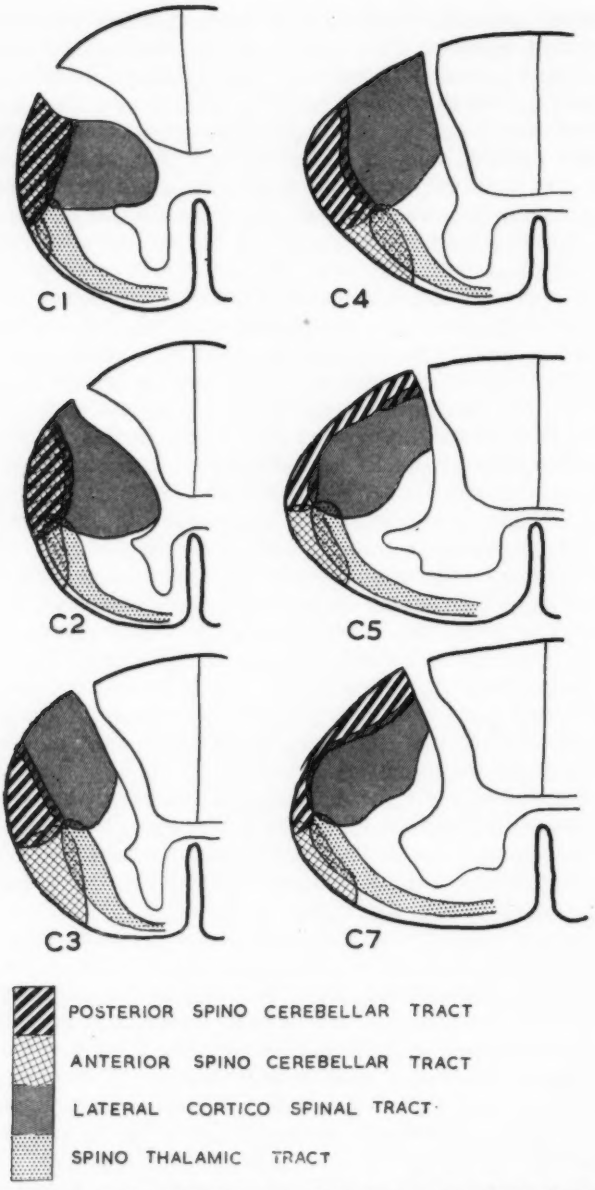

FIG. 13.—Diagram to show the location of the long tracts of the lateral column at different segmental levels of the human cervical cord.

each other at different segmental levels. Between the eighth and the fifth cervical segments the arrangement of the tracts remains much the same. Individual fibres in the groups alter their relationship to each other, and there are changes in the constitution of the tracts, but the general topography remains constant. In these segments the posterior and the anterior spino-cerebellar tracts form a continuous band along the periphery of the cord from the posterior horn to about the level of the most lateral of the anterior nerve roots. The posterior fibres form the part of this band which lies posterior to the level of the central canal; the anterior fibres form the anterior part. Medial to the posterior spino-cerebellar tract lies the lateral cortico-spinal and associated tracts; medial to the anterior spino-cerebellar tract lies the spino-thalamic and associated tracts. In the fourth and third cervical segments the spino-cerebellar tracts are massed more closely and, together with the spino-thalamic fibres, extend farther medially. In the postero-lateral zone cortico-spinal fibres come to the surface. In the second and first cervical segments both the posterior and the anterior spino-cerebellar fibres shift posteriorly, the anterior fibres mingling together with the posterior fibres, and the spino-thalamic fibres move slightly laterally and posteriorly.

There are then three patterns of fibre distribution in the lateral column of the cervical cord: that in the first and second segments, that in the third and fourth segments and that in the fifth to eighth segments.

Discussion

The usual diagram utilized in textbooks to demonstrate the arrangement of the fibres in the lateral column shows the location of the fibres to be approximately as has been shown here to obtain in the lower cervical segments. It has now been demonstrated that this is only one of the three patterns of fibre distribution in the cervical cord. The question may be raised why these findings have not been universally observed before. Certain features of the changing pattern of the fibres have in fact been noted by earlier workers. Flechsig (1876) showed that the lateral cortico-spinal tract occupies the most posterior part of the postero-lateral column in the upper cervical cord. This feature was incorporated in many of the older textbooks (e.g., Thomas, 1897; Barker, 1899). Modern anatomists have noted the peripheral location of some of the cortico-spinal fibres in experimental mammals (e.g., Verhaart, 1954; von Beusekom, 1955). Nevertheless it is rarely recognized in modern literature that in some part of its course in the human cervical cord the lateral cortico-spinal tract lies on the extreme periphery of the cord.

With respect to the spino-cerebellar tracts, these are most commonly described as being contiguous, but nevertheless independent and different in their spinal course. A few workers have described a gradual transference of some fibres from the anterior to the posterior tract in man (Barbacci,

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1891; Rossolimo, 1898) and in experimental mammals (Schäfer, 1899; Schäfer and Bruce, 1907; Schäfer, 1908; Bruce, 1910) but this has been refuted by other workers (Yoss, 1952). The rapid and marked posterior shift of most of the anterior fibres in the upper cervical cord and their almost complete intermingling with the posterior fibres described here has not been reported previously. The course of the spino-cerebellar fibres is being reported in more detail elsewhere (Smith, in press). There appear to be two principal reasons why this part of the course of the anterior spino-cerebellar tract has not been observed before. First, the fact that most human anatomical studies have been made on material with gross lesions implicating most of the tracts in the spinal cord. In such material details of single tracts cannot be determined. Secondly, unless all segments of the cord are examined, the systematization of the tracts in one segment is mistakenly assumed to be typical of all the segments in the region, and hence the changes in location of the tracts is unnoticed.

A knowledge of the changing and precise location of the tracts at different segmental levels is necessary in the interpretation of certain experimental and clinical findings. This may be illustrated by the following examples. It is customary to apply the results of physiological experiments in laboratory animals to man. For example the assumption is made that stimulation of certain regions of the cord would affect fibres of a certain tract. This assumption may be based on false premises. Again, for the purpose of determining the relations of fibres from different parts of the body to each other in the cord, the pattern of degeneration in different cases may be compared. But unless it is appreciated that exactly the same level of the cord must be compared in each case, fallacies may arise. For even within one segment, and this is particularly striking in the fifth and the second cervical segments, there is a considerable difference in the arrangement of the fibres in the caudal from that in the cranial part of the segment. Unless this is known, an interpretation may be made on apparent differences in the fibre pattern in two cases, when these differences are due solely to the variation in the segmental levels compared. And finally, in estimating the probable site of a lesion in the cervical cord, the knowledge of the three patterns of the fibres at different levels may be of some value. Fig. 14 shows which fibres would be primarily affected by pressure from a space-occupying lesion lying against the cervical cord in the postero-lateral region. It would be naïve to suggest too direct a relationship between direct pressure from a tumour, for example, and the resultant symptoms, ignoring all the complications of vascular disturbances and transmitted pressure. Nevertheless, the variation in the underlying fibres, in a short length of cord, is sufficiently marked to deserve comment. In the first and cranial part of the second cervical segments the fibres medial to the tumour are a mixture of so-

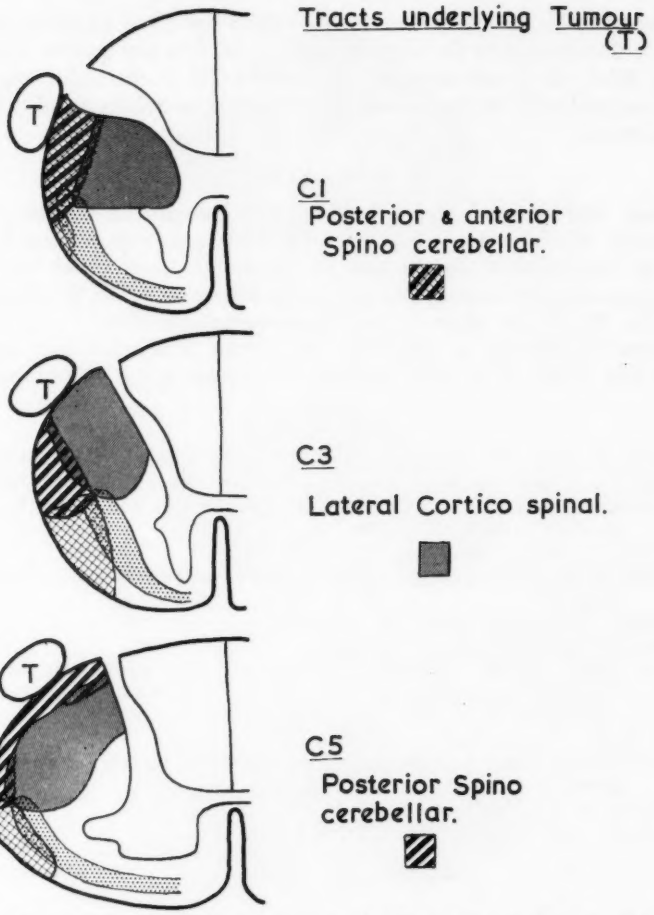

FIG. 14.—Diagram to show the variation in the fibres underlying a hypothetical tumour at different segmental levels in the cervical cord.

called posterior and anterior spino-cerebellar fibres, in the caudal part of the second and in the third and fourth segments lateral cortico-spinal fibres, and in the fifth and lower cervical segments, posterior spino-cerebellar fibres.

SUMMARY

A study has been made of the pattern of the long tracts of the lateral column of the human cervical cord.

It has been found that the location of the tracts varies in different

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segmental levels to such an extent that there are three separate patterns of fibre distribution in the cervical cord: in the first and second segments, in the third and fourth segments, and in the fifth to the eighth segments. The practical value of the knowledge of the precise behaviour of the tracts is discussed.

ACKNOWLEDGEMENTS

Many neurologists, neurosurgeons and pathologists have made possible the study, of which this is one small part. My gratitude is given to them all. In particular I should like to thank Dr. Carmichael for all his encouragement and advice and Mr. Wylie McKissock, Dr. W. Blackwood and Dr. W. G. P. Mair for their generous co-operation. I am deeply indebted to Mrs. J. A. Mills and Mr. Peter Sharp for their technical work and to Mr. J. A. Mills and Mr. L. Frampton for the photography.

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LEGEND FOR PLATES XXIV–XXXI

All the photographs are from Marchi preparations except Figs. 2 and 3, which are Weigert Pal preparations.

The figures are intended as a direct illustration of the text, and therefore no further descriptions of the figures are given.

PLATE XXIV

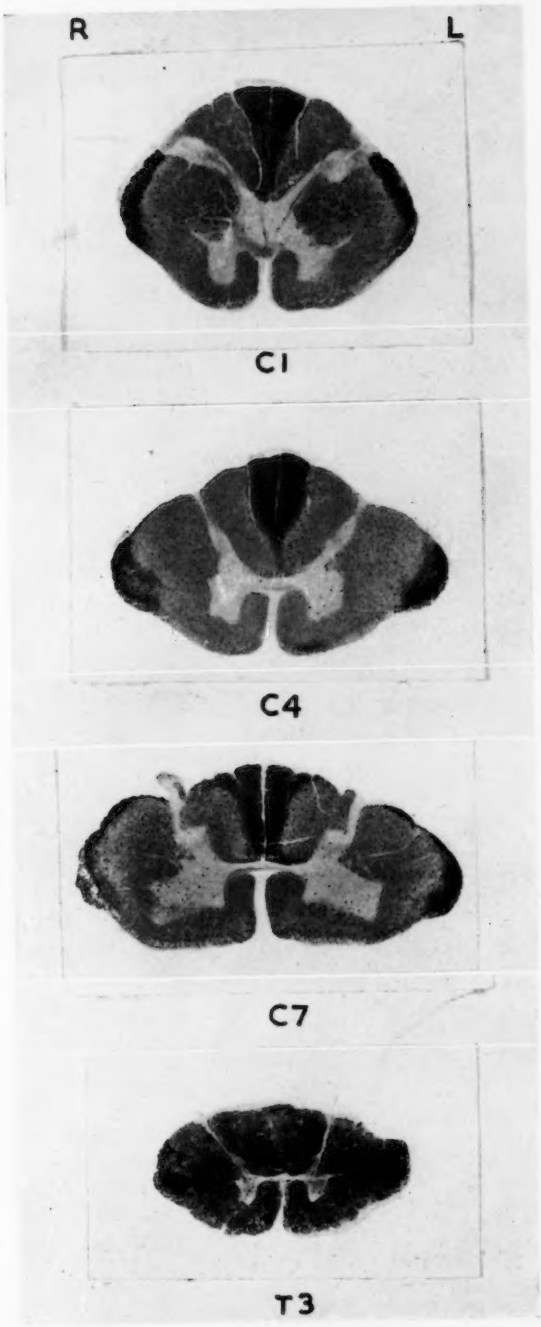

FIG. 1.

To illustrate article by Marion C. Smith.

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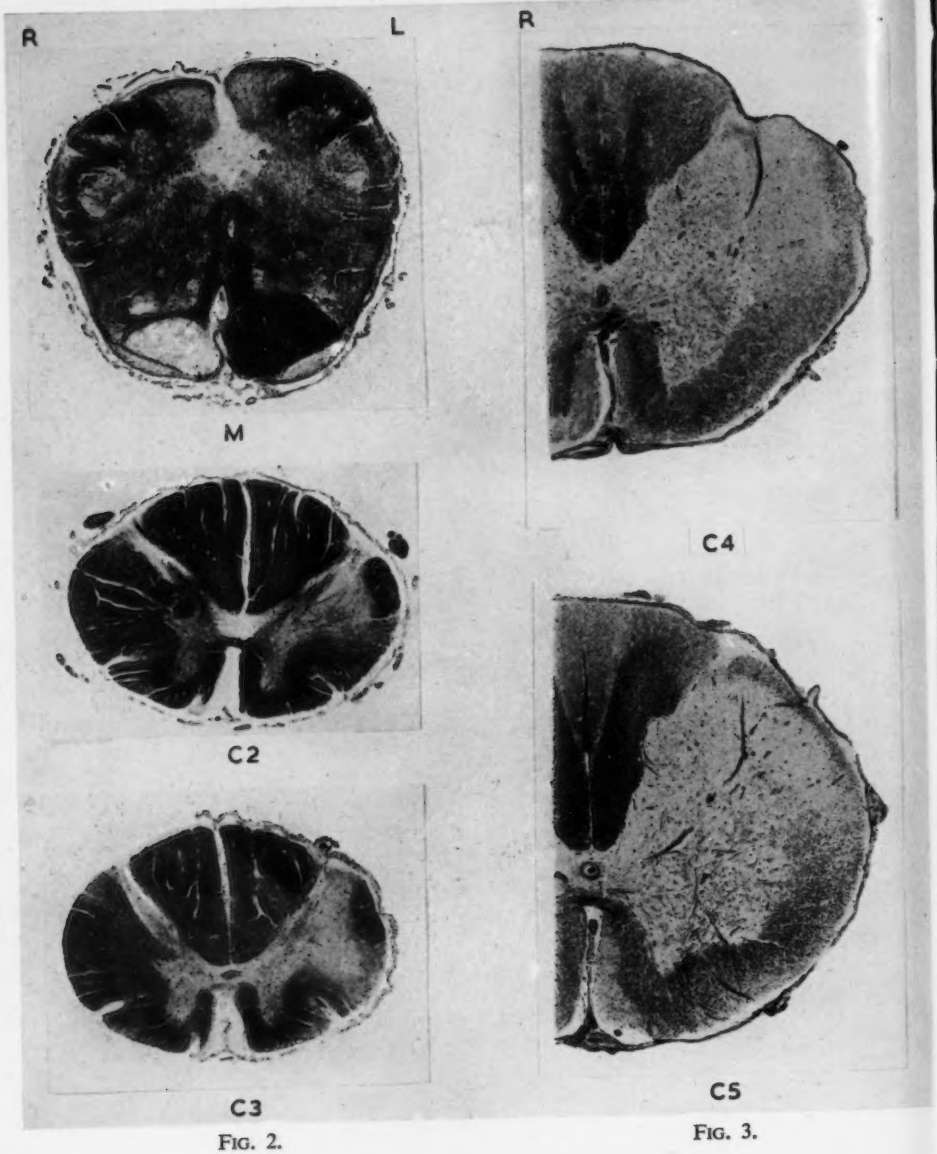

FIG. 2.

FIG. 3.

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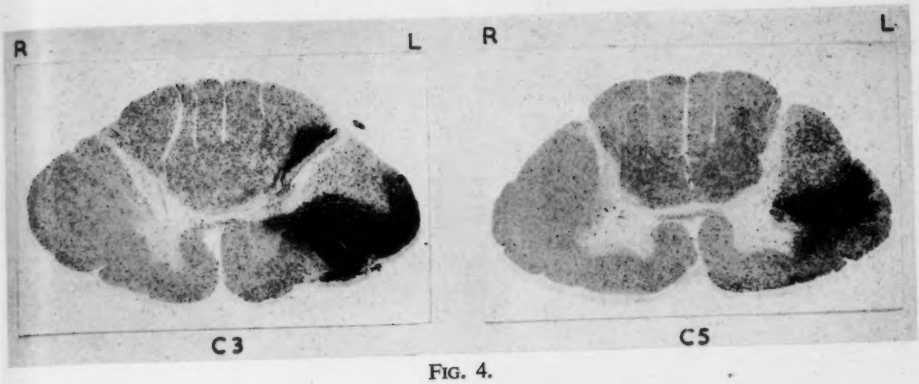

FIG. 4.

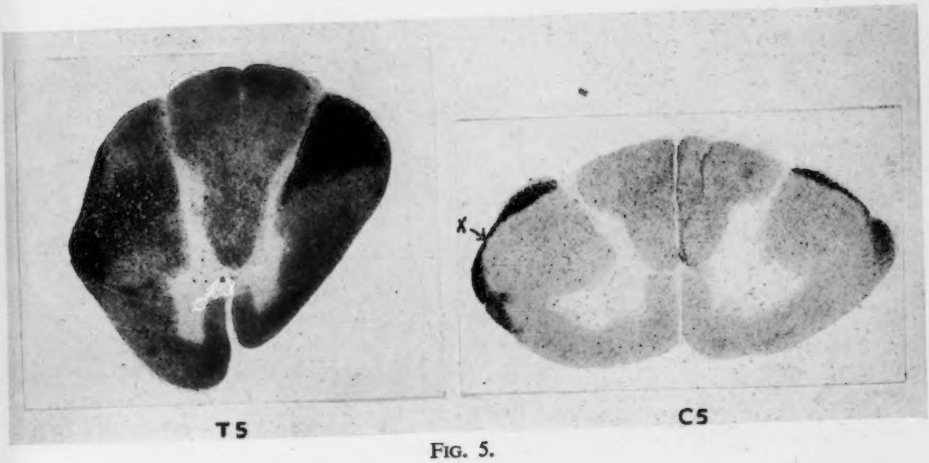

FIG. 5.

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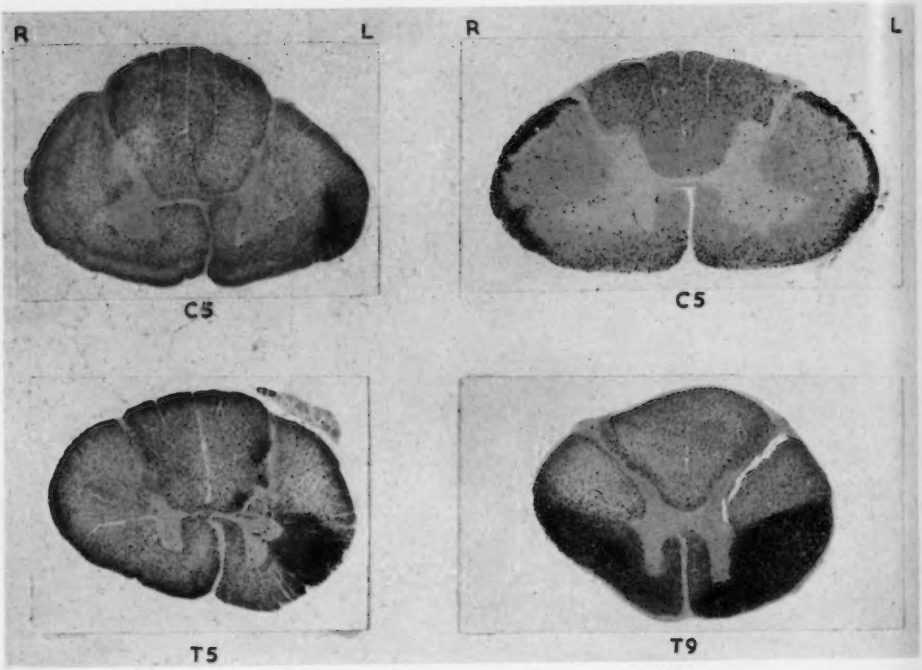

FIG. 6.

FIG. 7.

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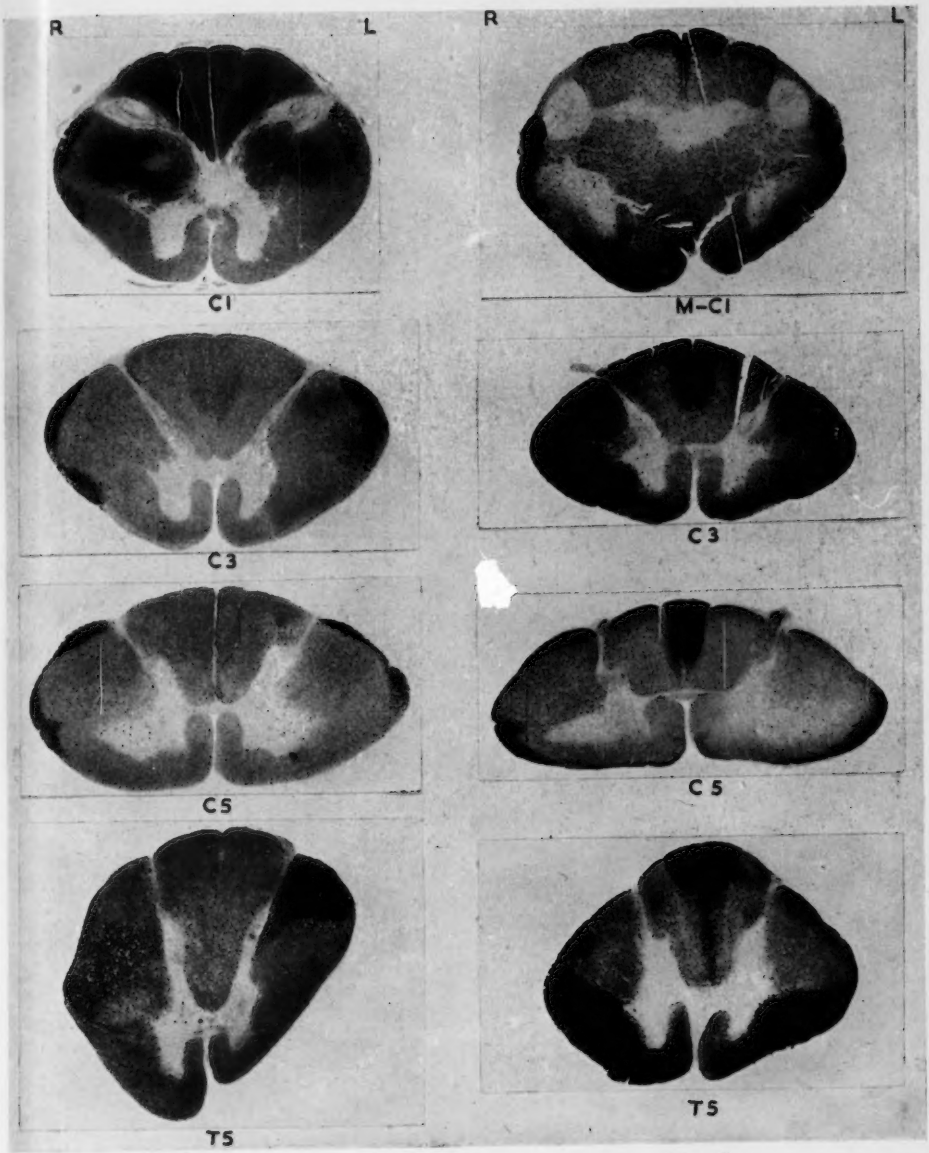

FIG. 8.

FIG. 9.

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PLATE XXIX

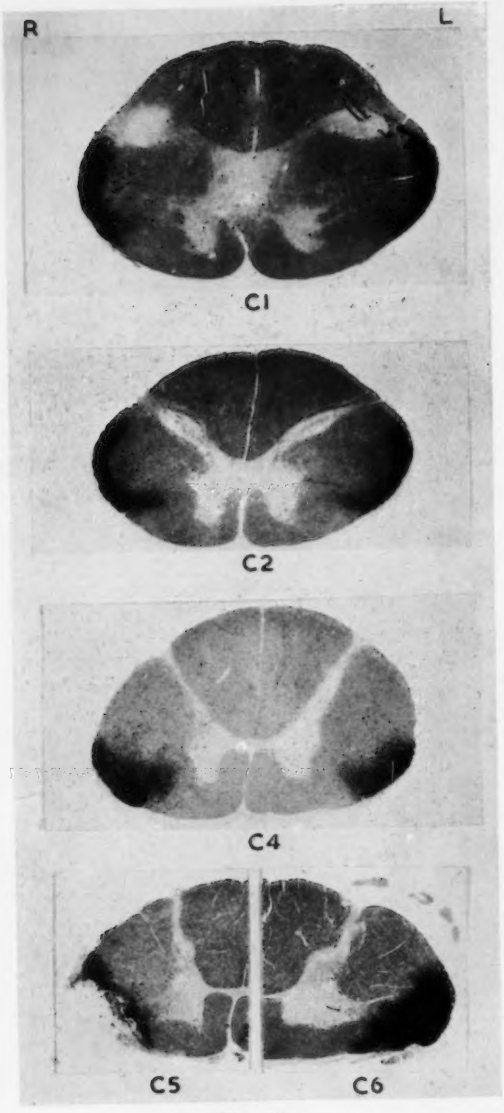

FIG. 10.

To illustrate article by Marion C. Smith.

PLATE XXX

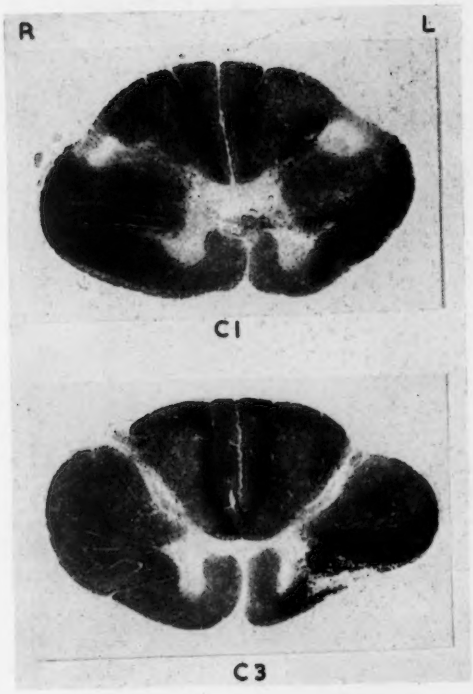

FIG. 11.

To illustrate article by Marion C. Smith.

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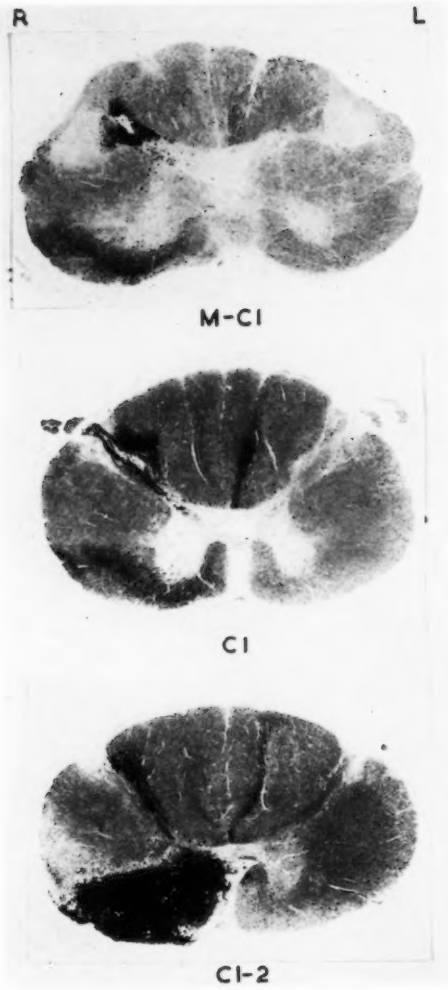

FIG. 12.

To illustrate article by Marion C. Smith.

CORTICOFUGAL FIBRES TO THE NUCLEI OF THE DORSAL COLUMNS

An Experimental Study in the Cat

BY

FRED WALBERG

Anatomical Institute, University of Oslo, Norway

Introduction

In a recent anatomical study Brodal, Szabo and Torvik (in press) have shown that following lesions of widespread regions of the cerebral cortex in the cat, terminal degeneration is present in all subdivisions of the sensory trigeminal nucleus and the nucleus of the solitary tract. The authors do not commit themselves as to the course of these corticofugal fibres to the sensory cranial nerve nuclei, but some of their observations favour the assumption that the fibres descend among those of the pyramidal tract. They also consider it likely that the corticofugal fibres may mediate the physiologically observed inhibitory effects on the central propagation of afferent messages through the trigeminal nucleus described by Hernández-Peón and Hagbarth (1955) and Hernández-Peón and Scherrer (1955). The termination of corticofugal fibres in the different subdivisions of the sensory trigeminal nucleus and in the nucleus of the solitary tract suggests that the cortical effects on central transmission may involve different kinds of somatic as well as visceral impulses.

In view of these findings it was deemed worth while to investigate whether also the nuclei of the dorsal columns receive corticofugal fibres, and if so, to map the exact termination of these fibres within the nuclei. Although the course and termination of the fibres ascending in the dorsal columns have been mapped in great detail (Ranson, Davenport and Doles, 1932; Pass, 1933; Ferraro and Barrera, 1935; Chang and Ruch, 1947; Escolar, 1948; Glees, Livingston and Soler, 1951 and Liu, 1956) a perusal of the available literature gives little information as to whether fibres descending from higher levels of the brain reach the nuclei of the dorsal columns. Probst (1903) states that following hemisection of the tegmentum in cats, degenerating fibres can be followed in Marchi-preparations from the pyramidal tract to these nuclei. Kuypers (1956) in silver preparations in the cat observed corticofugal fibres which leave the pyramidal tract and bend dorsally towards the dorsal column nuclei. In numerous other papers dealing with corticofugal projections to the

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brain-stem no mention is made of such fibres. In this connexion it is of some interest to note that Probst concluded by saying: "Diese Degenerations-produkte (in the dorsal column nuclei) stehen in unmittelbarem Zusammenhang mit den degenerierten Pyramiden die ventral von den Hinterstrangkernen in den Seitenstrang hinüberkreuzen. Es wäre allerdings sonderbar, dass die degenerierte Pyramidenbahn hier Fäserchen and die sensiblen Hinterstrangkerne abgäbe, es wäre aber nicht ganz unmgölich, dass hier eine Schaltung zwischen sensiblen und motorischen Neuronen stattfände." As will be seen below, Probst's suggestion was correct.

Material and Methods

Altogether 15 adult cats were employed as experimental animals. 4 cats served as normal controls.

In the experimental animals lesions were made of the cerebral cortex with sterile precautions under pento-barbital anæsthesia. Different parts of the cortex were destroyed with a knife and sucker or by thermocoagulation.

The animals were killed by exsanguination under chloroform or pento-barbital anæsthesia after six to twelve days. One animal was kept for seventy days. The brain and the spinal cord were then either immediately dissected free and fixed by immersion in formalin or formol-saline or the animal was perfused with formalin intravitally.

The lesion in the cerebral cortex was mapped macroscopically and its extent was controlled under the microscope.

The occurrence of degenerating terminal fibres and boutons was studied in horizontal or sagittal frozen sections (15 μ thick) through the brain-stem, prepared according to the Glees' (1946) method, or the method of Nauta and Gygax (1951). The blocks were cut serially, and sections were selected with approximately equal intervals for staining and subsequent mounting.

The brain-stems of the 4 normal animals were prepared in the same manner and served as controls for the study of degenerating fibres and boutons in the experimental material. In none of them was there any appearance of terminal degeneration in the dorsal column nuclei. A complete series of Nissl stained horizontal sections and some series of transverse Glees or Nissl stained sections through the brain-stem were used to facilitate the identification of the nuclei of the dorsal columns in the experimental animals.

Most of the material on which this investigation is based has been used also for the tracing of afferent fibres to the inferior olive (Walberg, 1956).

Observations

Following lesions of various regions of the cerebral cortex, degenerating terminal fibres and boutons have been found in the nuclei of the dorsal columns, i.e. the cuneate and gracile nuclei, while the external cuneate nucleus has always been found free from degeneration. Terminal degeneration is present throughout almost the entire extent of the nuclei with a clear-cut maximum in their rostroventral parts (*vide infra*). Before describing the results obtained a brief account of the appearance of the degenerative changes in terminal fibres and boutons will be appropriate. A detailed description of the nucleus gracilis and cuneatus as they appear

in silver stained sections is omitted, since this has been given in a recent publication by Glees and Soler (1951).

Terminal Degeneration in the Nuclei of the Dorsal Columns

The term "terminal degeneration" is used here to denote the degenerative changes which occur in terminal boutons and in fine terminal nerve fibres following transection of the parent fibre. The changes observed in the nuclei of the dorsal columns in the present study correspond to those found when lesions have been made of the dorsal funiculi in the spinal cord. However, the number of terminal degenerating particles following even extensive cortical lesions is small as compared with the massive degeneration following lesions of the dorsal columns.

The degenerating terminal fibres usually appear as longer or shorter rows of argentaffin, ovoid to globule-shaped, distinctly stained black dots (figs. 4A–E). Sometimes the dots have a more irregular shape. The degenerating boutons show an increased affinity for silver and their form is frequently irregular. Sometimes a terminal fibre can be followed to a bouton, but more usually this is not possible. The degenerating terminal fibres are found to make contact with cell processes as well as with perikarya. A relation to cell processes is less frequently seen than contacts with perikarya.

It is well known that in silver impregnated sections of normal material terminal boutons may frequently appear in different forms, some of which may be misinterpreted as representing degenerating boutons. This is the case for example in the inferior olive and in the reticular formation of the brain-stem (Brodal, Walberg and Blackstad, 1950; Rossi and Brodal, 1956 and Walberg, 1956). In order to avoid errors due to misinterpretations of boutons, in the present study an area has never been considered as the site of "terminal degeneration" unless it contains in addition to degenerating boutons also characteristic degenerating fine terminal fibres.

Most of the animals used in this study have been killed within nine days after the making of the lesion. However, it is of interest to mention that even after a survival period of seventy days, terminal degeneration is still present in the nuclei of the dorsal columns (cat 2728, lesion of the sensorimotor cortex, *see* fig. 4A). Even if the amount of degeneration is comparatively small, this finding shows that in the central nervous system remnants of degenerating terminal fibres may be preserved longer than is generally assumed.[1]

My material, however, does not permit detailed statements concerning the role of the time factor in central nerve fibre degeneration, except for saying that in the nuclei here studied terminal degeneration appears to be clear-cut from about six days after a cortical lesion.

[1]Terminal degeneration is also present in other nuclei of the central nervous system in this animal, e.g. in the pontine nuclei and in the inferior olive.

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The majority of the fibres descending to the nuclei of the dorsal columns probably end there, since most of the degenerating fibres observed are either terminal or preterminal. More seldom a coarser degenerating fibre is seen within the nucleus.

Representative Experimental Cases

In the diagrams to be presented below of the findings in representative cases, the occurrence of terminal degeneration within the nuclei of the dorsal columns will be indicated by dots, the density of the dots giving an impression of the intensity of terminal degeneration. Some experi-

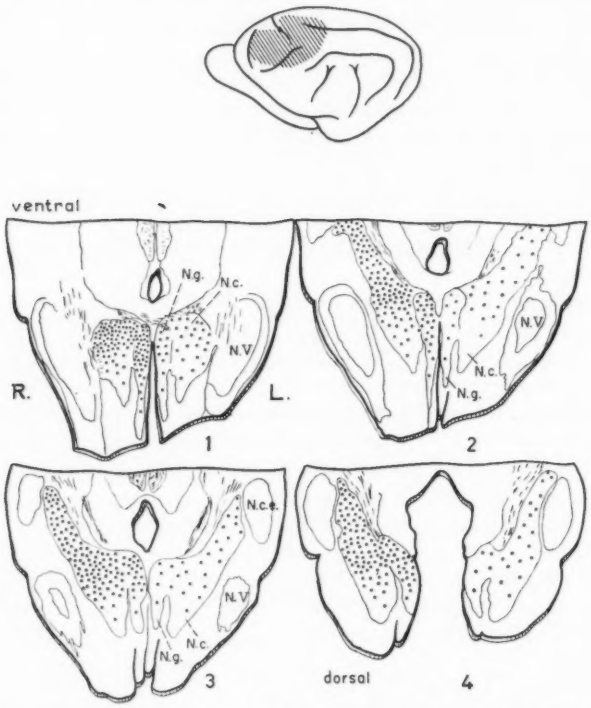

FIG. 1.—Diagrammatic presentation of the findings in cat B.St.L. 14. Above, a lesion (hatchings) in the fronto-parietal region of the left hemisphere. Below, a series of drawings of horizontal sections through the brain-stem showing the distribution of terminal degeneration (dots) in the dorsal column nuclei following the lesion. Terminal degeneration is present in the dorsal column nuclei on both sides, but much more marked on the contralateral side. Note absence of degeneration in the external cuneate nucleus. Abbreviations for all figures: L.: left. N.c.: nucleus cuneatus. N.c.e.: nucleus cuneatus externus. N.g.: nucleus gracilis. N.V.: nucleus of spinal tract of trigeminal nerve. R.: right.

ments will be described and illustrated and others will be mentioned more briefly to illustrate the distribution of terminal degeneration in the nucleus gracilis and cuneatus following various lesions of the cerebral cortex.

Cat B.St.L. 14. *Killed after* 8 *days* (*fig.* 1).

With knife and sucker a lesion was placed in the frontoparietal region of the left hemisphere. The bulk of the lesion lies in the anterior and posterior sigmoid gyri. The adjacent part of the lateral and anterior suprasylvian gyri, and, to a lesser extent, the gyrus proreus, are also affected. The lesion involves the underlying white matter, without, however, destroying other structures of the brain.

In the silver impregnated sections, typical terminal degeneration of fibres and boutons is seen in the nuclei of the dorsal columns on both sides. The degeneration is much more pronounced on the right (contralateral) side, as indicated by the density of dots in the diagram of fig. 1. The maximum of degeneration is found in the rostral half of the nuclei, while the caudal part contains only few terminal fibres and boutons. There is a gradual decrease in degeneration when passing in a rostro-caudal direction and no distinct "border" between regions receiving or not receiving terminal degeneration, as for example in the inferior olive following lesions of the cerebral cortex (Walberg, 1956). The degeneration seems to be more pronounced ventrally than dorsally, and the number of terminal fibres and boutons seems to be larger in the nucleus cuneatus than in the nucleus gracilis. No degenerating structures are present in the external cuneate nuclei.

Corresponding findings were made in another case, cat B.St.L. 73, killed seven days after a similar lesion of the fronto-parietal cortex (fig. 2A).

These experiments demonstrate that fibres pass from the fronto-parietal region of the cerebral cortex to the nuclei of the dorsal columns and also that more corticofugal fibres reach the contralateral than the homolateral nuclei. The terminal degeneration is most abundant in the rostral and ventral regions of the nuclei.

In the above experiments "motor" as well as "sensory" cortical areas have been removed. On account of the well-known lamination within the termination of the spinal afferents to the nuclei of the dorsal columns (fibres from sacral, lumbar and lower thoracic levels ending in the nucleus gracilis, those from upper thoracic and cervical levels in the nucleus cuneatus (Ranson, Davenport and Doles, 1932; Pass, 1933; Ferraro and Barrera, 1935; Chang and Ruch, 1947; Escolar, 1948 and Glees, Livingston and Soler, 1951), it is of interest to study the terminal distribution of fibres in these nuclei following lesions involving separately the cortical fore- and hind-limb area. In cats B.St.L. 12 and 13 (figs. 2B and C) the fore-limb and hind-limb area, respectively, were removed following determination of the regions in question by electrical cortical stimulation.[1] Both animals were killed eight days after the operation. The distribution of terminal fibres is the same in the 2 cases, and apart from the fact that terminal degeneration is more scanty, the findings in the 2 cases correspond to the findings in cat B.St.L. 14 (fig. 1), the distribution of terminal degeneration

[1]The lesion in cat B.St.L. 13 extends a little on the medial side of the hemisphere, not shown in the diagram.

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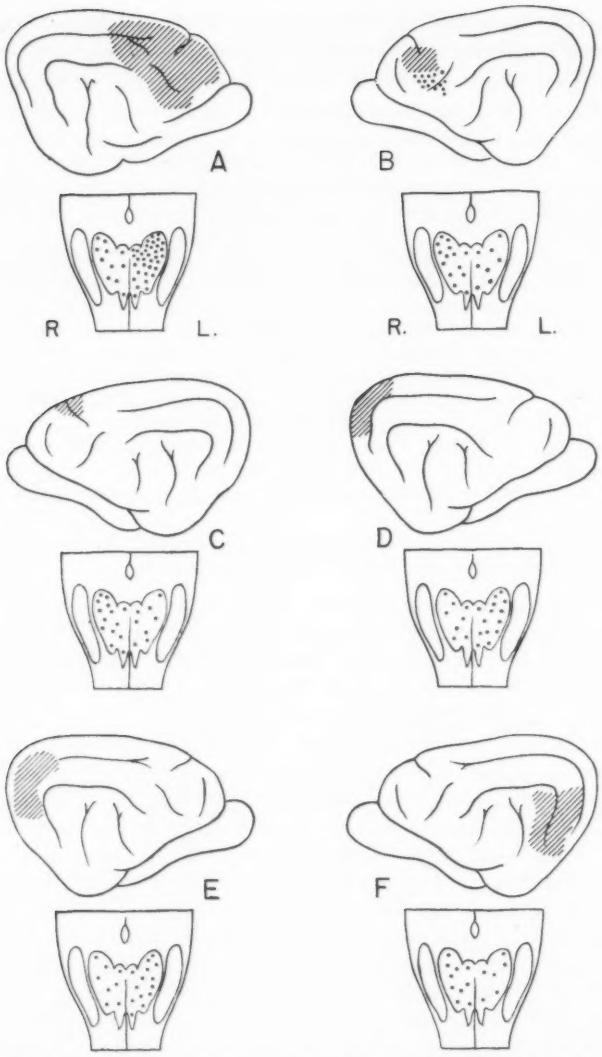

FIG. 2.—Diagrams showing lesions (hatchings) in various regions of the cerebral hemisphere in cats B.St.L. 73, 12, 13, 30, 31 and 37. A–C: lesions in the fronto-parietal region, D–F: lesions in the temporo-occipital region of the cortex. The dots in figure B indicate areas the fibres from which have been interrupted. Below each diagram of the hemisphere a drawing showing the relative intensity of terminal degeneration (dots) in the dorsal column nuclei. Note absence of terminal degeneration in the external cuneate nucleus. Abbreviations as in fig. 1.

being similar. Thus no somatotopical arrangement could be established within the termination of the descending fibres.

Unfortunately no cases with lesions restricted to "sensory" areas behind the "motor" are available. However, since the terminal degeneration is less intense in the 2 cases just described than in the cases with large fronto-parietal lesions, it appears likely that not only the "motor" but also the "sensory" areas project on to the nuclei of the dorsal columns.

The projection from the occipital and temporal cortices to the dorsal column nuclei is more modest than that from the fronto-parietal region. 5 relevant cases are shown in figs. 2D–F and 3A–B. In cat B.St.L. 30 (killed after six days) a lesion was made in the region of the right striate area. Only the adjacent part of the white matter is affected. In cat B.St.L. 31 (killed after six days), the lesion is somewhat larger, including the area 19s of Garol (1942) and part of the lateral gyrus. On account of some bleeding the adjacent white matter underneath the posterior part of the ectosylvian gyrus is also destroyed. In cat B.St.L. 37 (killed after six days), the lesion involves the posterior suprasylvian and the posterior ectosylvian gyri and some of the underlying white matter. In two other cats the lesion lies in the temporal region of the hemisphere. In cat B.St.L. 8 (killed after seven days) the lesion involves parts of the middle and posterior ectosylvian gyri and the anterior sylvian gyrus, in cat B.St.L. 29 (killed after six days) the lesion is a little more restricted but otherwise almost similar to that in the case just described. In all these cases terminal degeneration is present in the dorsal column nuclei on both sides. As is the case with the fronto-parietal lesions, the degeneration is more abundant in the contralateral nuclei. However, when the different series are compared it is learnt that lesions of the occipital region produce a more marked terminal degeneration in the dorsal column nuclei than lesions of the temporal region. On the other hand, in none of the cats with temporo-occipital lesions is the terminal degeneration as abundant as following lesions of the fronto-parietal region of the hemisphere.

Also the medial and basal surfaces of the cerebral hemisphere send fibres to the dorsal column nuclei. Two relevant cases are shown in figs. 3C and D. In cat B.St.L. 104 (killed after nine days) the lesion includes most of the suprasplenial, splenial and cingulate gyri, and also axons from cells in the anterior part of the lateral gyrus and the adjacent part of the posterior sigmoid gyrus have been cut (dots in fig. 3C). In cat B.St.L. 79 (killed after seven days) the lesion on the basal surface extends from the frontal to the occipital region of the brain, including the inferior part of the anterior ectosylvian and orbital gyri, extending into the adjacent part of the anterior and posterior sylvian gyri and also including the greater part of the piriform lobe. Posteriorly, the lesion involves a small part of the dorsal region of the lateral and posterior

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sylvian gyri. In both cases terminal degeneration is found bilaterally in the dorsal column nuclei and, as in the preceding cases, it is most intense in the nuclei on the side contralateral to the lesion. The degree of degeneration is similar to that seen in cases with occipital lesions. It seems to be

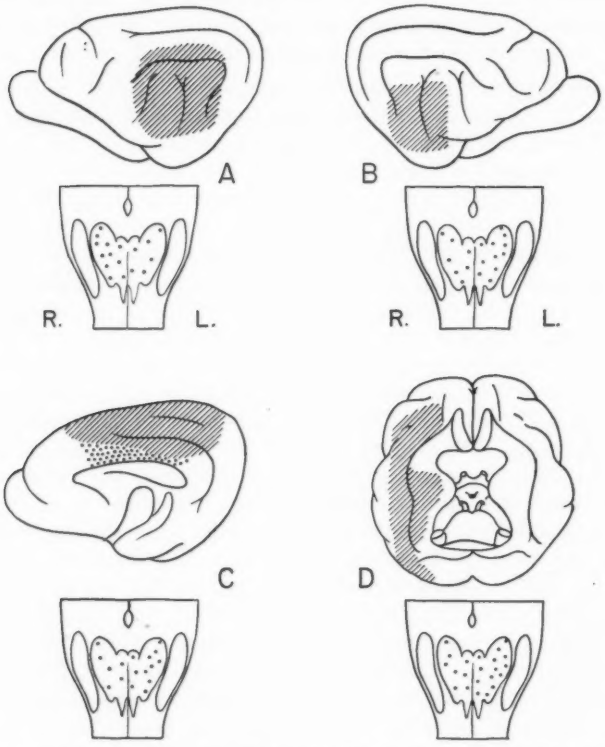

FIG. 3.—Diagram showing lesions (hatchings) in various regions of the cerebral hemisphere in cats B.St.L. 8, 29, 104 and 79. A–B: lesions in the temporal region, C: lesion on the medial surface, D: lesion on the basal surface of the cortex. Below each diagram of the hemisphere a drawing showing the relative amount of terminal degeneration (dots) in the dorsal column nuclei. Note absence of terminal degeneration in the external cuneate nucleus. As in the preceding figure, the dots in fig. 3C indicate areas the fibres from which have been interrupted. Abbreviations as in fig. 1.

a little more marked following lesions of the basal than of the medial surface of the brain. In 2 other cats (B.St.L. 48 and 75, killed after six and seven days respectively, illustrated in Walberg, 1956) having an anterior and a posterior basal lesion, respectively, the amount of terminal

degeneration in the dorsal column nuclei is of approximately the same intensity.

Quantitative estimates of terminal degeneration in silver-stained preparations are uncertain, among other things because of the capriciousness of the silver methods. However, the clear-cut and consistent quantitative differences observed between cases with certain types of lesions, make clear that the fronto-parietal region supplies the dorsal column nuclei with a greater number of fibres than does any other region. The temporal region of the hemisphere gives origin to the smallest amount of corticofugal fibres, whereas the occipital, medial and basal surfaces have a more ample contribution.

It remains to consider along which routes the corticofugal fibres to the dorsal column nuclei descend. Kuypers (1956) describes recurrent pyramidal tract fibres which pass ventrally to the dorsal column nuclei. Since in the cat there is some intermingling of the fibres of the pyramid and those of the medial lemniscus, as recently emphasized by Glees, Liddell and Phillips (1951), there is a possibility that fibres from the pyramidal tract might leave this and join the medial lemniscus during its course in the medulla. In cat B.St.L. 110 (killed after 12 days, not illustrated), where a lesion was made in the right fronto-parietal region, the medulla was cut sagitally, in order to facilitate the tracing of the fibres of the two tracts. Degenerating fibres are found not only in the pyramidal tract but also in the right medial lemniscus, ventral and rostral to the inferior olive (*see* figs. 4 F–G). The degenerating fibres in the medial lemniscus are mostly very thin. Close to the dorsal column nuclei the lemniscal fibres are best seen in the horizontally cut series where they appear as strands of fibres coursing obliquely towards the raphe. Also here some degenerating fibres are found. It appears, therefore, that at least part of the corticofugal fibres to the dorsal column nuclei descend in the pyramidal tract and enter the medial lemniscus at medullary levels.[1] They then follow the lemniscus to the dorsal column nuclei. However, it is also seen from the sections that a certain number of corticofugal fibres to these nuclei enter them as descending fibres. Most of these fibres are coarser than those found in the medial lemniscus. Probably they descend within the reticular formation, after having left the pyramidal tract.

Discussion

Degenerative changes in the dorsal column nuclei following cortical lesions.—The degenerative changes observed in the dorsal column nuclei in the present experimental material largely conform with those described

[1]It has been shown in the cat that pyramidal tract fibres are derived not only from the fronto-parietal region but from the temporo-occipital region of the cortex as well (Walberg and Brodal, 1953), and it appears that also the medial and basal surface of the brain contribute to the pyramidal tract (unpublished observations).

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in the same nuclei by Glees and Soler (1951) following sections of the dorsal roots or lesions of the dorsal columns. However, in addition to the coarse degenerating terminals described by these authors the terminal endings of fibres may also appear as longer or shorter rows of argentaffin, ovoid to globule-shaped, distinctly stained black dots (*see* photomicrographs in figs. 4A–E). Sometimes these terminal fibres can be followed to a bouton, but frequently this is not possible. These findings, however, cannot be taken as evidence that some cortical fibres to the dorsal column nuclei lack terminal boutons. On the other hand it is of interest to recall that Scheibel and Scheibel (1955) in their Golgi-material show terminals ending without boutons in the inferior olive, and that they describe at least four different types of afferent terminals within this nucleus. Even if nothing is known as to the finer structure of the terminals of the corticofugal fibres to the dorsal column nuclei, findings like these indicate that different types of terminals may virtually exist also within these nuclei.

Concerning the place of contact between terminal fibres and cells, axo-somatic connexions are by far the most abundant (figs. 4A–E). However, some of the fibres from the cerebral cortex make contact with cell processes. This is particularly evident in the rostralmost part of the nuclei, where the fibrous feltwork is less dense than at more caudal levels. Glees and Soler (1951) in their paper mention that they have been able to study only the axo-somatic connexions of the posterior column fibres. However, in two series subjected to lesions of the spinal cord (Sp.C.L. 15 and 16, used for other purposes, *see* figs. 5 and 4 respectively in Brodal, Walberg and Blackstad, 1950), terminal fibres may be seen ending in the same manner in the dorsal column nuclei as do those coming from the cerebral cortex, i.e. not only on the perikarya but on cell processes as well. It cannot be decided whether the synapses between the terminal fibres and the cell processes are axo-dendritic only or also axo-axonic, since the distinction between axons and dendrites is usually impossible in Glees-sections.

Unless there are marked differences between two areas in the number of degenerating terminal fibres and boutons it is impossible to make quantitative comparisons. However, the difference between the dorsal column nuclei on the two sides in my cases is so marked that it is safe to conclude that far more fibres reach the contralateral nuclei than the ipsilateral.

The series of cat 2728 is of special interest for the question of the time factor in central nerve fibre degeneration. In this cat, killed seventy days after a bilateral ablation of the sensorimotor cortex had been made, there is still terminal degeneration in the dorsal column nuclei. Also coarser fibres entering the nuclei are found in a state of degeneration. Terminal structures, therefore, are able to "survive" much longer than is generally assumed, but whether this is generally valid for all fibre systems remains to be seen.

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Origin, course and termination of the corticofugal fibres.—The present study reveals that following various lesions of the cerebral cortex terminal degeneration is present within the dorsal column nuclei. The corticofugal fibres come from all major subdivisions of the cortex, the most important of these being the sensorimotor region. These quantitative differences probably reflect gradients of functional importance. Since almost all lesions include several areas, it is impossible to make definite statements as to which cytoarchitectural areas give origin to corticofugal fibres, but it is clear that the nuclei of the dorsal columns may be influenced from cortical areas which according to present knowledge are related to different "functions," e.g. the striate and acoustic areas, and areas related to so-called "suppressor" activity.

It is of particular relevance to the problem of somatotopical localization within the dorsal column nuclei that no evidence could be brought forward that the corticofugal fibres terminate in a somatotopical manner, as do the ascending fibres of the dorsal columns. A similar lack of somatotopical organization has been found for the corticofugal fibres to the inferior olive (Walberg, 1956), to the reticular formation of the pons and medulla (Rossi and Brodal, 1956) and to the sensory trigeminal nucleus and the nucleus of the solitary tract (Brodal, Szabo and Torvik, in press).

The fact that fibres from different cortical areas converge on the dorsal column nuclei points to these nuclei as being structures subserving a certain integration of various kinds of impulses. This assumption is strengthened by the finding that fibres from the various regions of the cortex all end throughout the whole nuclear complex. This observation corresponds to the findings by Brodal, Szabo and Torvik (in press) that fibres from various parts of the cerebral cortex pass to all subdivisions of the sensory trigeminal nuclei and the nucleus of the solitary tract.

As already mentioned, some of the fibres entering the dorsal column nuclei from the cerebral cortex descend in the medial lemniscus on the side of the lesion. These usually are very thin and can be seen to enter the medial lemniscus from the pyramidal tract at the level of the inferior olive where the pyramidal and lemniscal fibres intermingle (Glees, Liddell and Phillips, 1951). Mettler (1935*a*, 1935*b*, 1947) describes degenerating fibres in the medial lemniscus of monkeys following lesions of the frontal and temporal regions of the cerebral cortex. Levin (1936) does the same following lesions of the frontal region, and Kanki and Ban (1952) found degeneration in the medial lemniscus after frontal subcorticotomy in man. Degenerating fibres in the medial lemniscus following lesions of the cerebral cortex have been found also by many other students of corticofugal fibres in animals and man. No comment on these findings, which were all made in Marchi material, is made. However, judging from my findings in the cat it seems reasonable to assume that also in

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monkey and man corticofugal fibres may reach the nuclei of the dorsal columns *via* the medial lemniscus.[1]

Even if some of the corticofugal fibres to the dorsal column nuclei pass in the medial lemniscus it is, nevertheless, obvious from my findings that a certain number descend in the reticular formation, from which they enter these nuclei. Whether these fibres are ultimately derived from the pyramidal tract cannot be said, but this seems likely from the findings of Probst (1903) and Kuypers (1956).

Functional considerations.—The finding of corticofugal fibres to the dorsal column nuclei invites speculations as to their possible functional significance. According to clinical and experimental data the primary sensory fibres ending in the dorsal column nuclei mediate impulses of cutaneous as well as proprioceptive origin. Brodal, Szabo and Torvik (in press) recently found fibres from the cerebral cortex terminating in all divisions of the spinal and principal trigeminal sensory nucleus and in the nucleus of the solitary tract. These corticofugal fibres, like those to the dorsal column nuclei, are derived from various parts of the cerebral cortex. There are good reasons to assume that different parts of the sensory trigeminal nucleus are related to the central transmission of pain, temperature and tactile impulses, and the nucleus of the solitary tract conveys, at least chiefly, impulses of visceral origin.

These anatomical findings indicate that the cerebral cortex, particularly its sensorimotor region, must be able to influence, in some way or other, the central transmission of impulses *via* the dorsal column nuclei, the trigeminal nucleus and the nucleus of the solitary tract. This effect must be exerted on sensory messages coming from a wide variety of receptors.

Some recent physiological studies are in agreement with this assumption. Thus Hernández-Peón and Hagbarth (1955) and Hernández-Peón and Scherrer (1955) observed inhibitory effects on the trigeminal afferent impulses following stimulation of the cerebral cortex. Scherrer and Hernández-Peón (1955), following electrical stimulation of the sensorimotor cortex, described depression or abolition of the postsynaptic potentials in the nucleus gracilis evoked by single shocks supplied to the corresponding dorsal column. It appears entirely possible that these effects may be mediated *via* the anatomically demonstrated corticofugal

[1]Dorsal to the crossing of the lemnisci there are also some degenerating fibres in the lemniscus on the ipsilateral side. Ventral to the crossing, however, degenerating fibres are found only in the lemniscus at the side of the lesion in the cerebral cortex. The degenerating fibres in the medial lemniscus on the ipsilateral side dorsal to the crossing, therefore, probably reach this where the crossing of the lemnisci takes place. It is interesting to recall in this connexion that in the pyramidal tract ascending fibres have recently been described (Brodal and Walberg, 1952), and that Rasmussen (1955) in silver preparations in cats mentions fibres passing from the inferior colliculus to the superior olive in the lateral lemniscus. Furthermore, Cajal (1910) has given description of centrifugal fibres in the olfactory and optic tracts. All these findings show that "two-way" tracts in the central nervous system may actually be more common than has hitherto been thought. A closer study of other tracts may give more information concerning this problem.

fibres even if a transmission along cortico-reticulonuclear pathways cannot be excluded.

Another point of functional interest concerns the mode of termination of the corticofugal fibres to the dorsal column nuclei. These fibres, as described above, establish synaptical contact with cell bodies as well as with cell processes. There appears to be a growing body of evidence that there may be important functional differences between axosomatic and axodendritic synaptical contacts. The anatomically demonstrated modes of termination of the afferent fibres might, therefore, deserve attention in future physiological studies.

It is worthy of notice that the external cuneate nucleus does not receive corticofugal fibres. It even appears doubtful whether it receives any fibres descending through the brain-stem at all, since no terminal degeneration is found in the nucleus following a hemisection of the brain at the pontine level (cat B.St.L. 71). The external cuneate nucleus, which like the gracile and cuneate nuclei receives its main afferents from the spinal cord (Ranson, Davenport and Doles, 1932; Pass, 1933; Ferraro and Barrera, 1935; Escolar, 1948, and Liu, 1956) contrary to these does not send its efferent fibres to the medial lemniscus but projects on to the "spinal areas" of the cerebellum (Brodal, 1941).

The findings made in this study are further indications that the external cuneate nucleus is functionally different from the gracile and cuneate nuclei. In addition they are evidence that not all primary sensory nuclei are subjected to influences from the cerebral cortex by direct corticofugal fibres.

Summary

The distribution of terminal degeneration within the dorsal column nuclei following lesions of various parts of the cerebral cortex has been studied by Glees' (1946) silver method.

After lesions of fronto-parietal, occipital, temporal, medial and basal regions of the cerebral cortex terminal degeneration is found in the nuclei cuneati and graciles while the external cuneate nucleus is free from degeneration. The majority of the corticofugal fibres to the nuclei cuneati and graciles are derived from the sensorimotor cortex. No evidence was found that the fibres from cerebral fore-leg and hind-leg areas terminate in a somatotopical manner.

The corticofugal fibres to the dorsal column nuclei descend with those of the pyramidal tract. Some of them leave the pyramid at the medullary level and enter the medial lemniscus, from which they finally reach the nuclei. Other fibres appear to pass through the reticular formation of the medulla on their way from the pyramidal tract to the nuclei.

After unilateral cortical lesions, terminal fibres and boutons are found bilaterally in the dorsal column nuclei. The majority of corticofugal

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fibres enter the contralateral nuclei. The terminal degeneration is present throughout the whole extent of the nuclei, but is most marked in their rostroventral parts. Terminal fibres and boutons are found on cell bodies as well as on cell processes.

For an evaluation of the time factor in central nerve fibre degeneration it is of interest to note that in one cat degenerating terminal fibres and boutons are present seventy days after the operation.

The functional significance of the findings is briefly discussed.

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PLATE XXXII

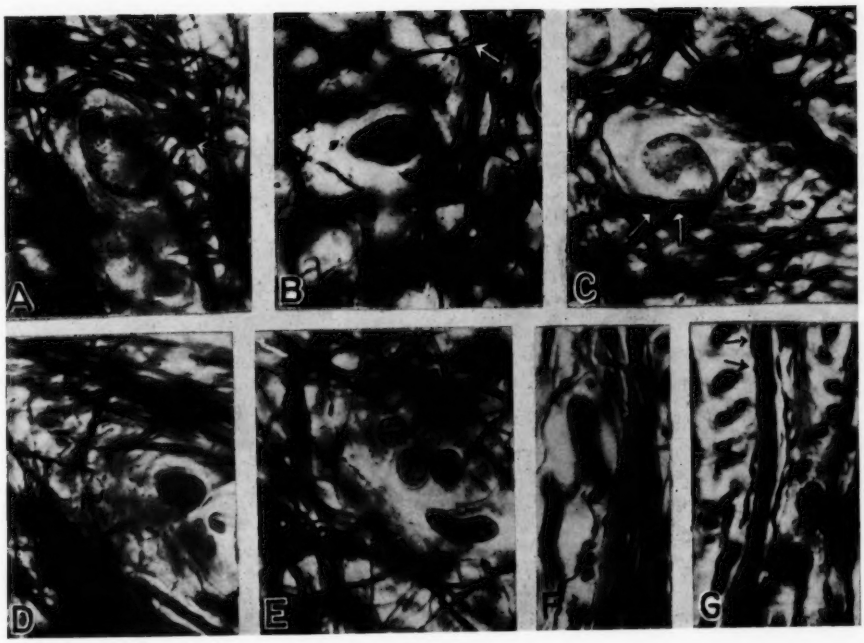

FIG. 4.

To illustrate article by ***F. Walberg.***

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LEGEND FOR PLATE XXXII

FIG. 4A–E.—Photomicrographs from the dorsal column nuclei of the cat showing terminal degeneration following lesions of the cerebral cortex. Glees method. ×1080. A: From the right nucleus cuneatus, seventy days after a bilateral lesion of the sensorimotor region (cat 2728). B: From the right nucleus cuneatus, eight days after a lesion of the left "hind-leg" area (cat B.St.L. 13, cp. fig. 2C). C, D and E: From the left nucleus cuneatus, nine days after a lesion on the medial surface of the right cerebral hemisphere (cat B.St.L. 104, cp. fig. 3C).

FIG. 4F–G.—Photomicrographs showing degenerating fibres in the right medial lemniscus at the level of the rostral pole of the inferior olive twelve days after a lesion of the right fronto-parietal region of the cerebral cortex (cat B.St.L. 110). Note small calibre of degenerating fibres. Glees method. ×1080.

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NOTICES OF RECENT PUBLICATIONS

LESIONS OF THE CERVICAL DISKS

Lesions of the Cervical Intervertebral Disk. By R. GLEN SPURLING, M.D., Professor of Neurosurgery, University of Louisville School of Medicine. Charles C. Thomas, Springfield, Illinois, U.S.A., and Blackwell Scientific Publications, Oxford. 1956. Pp. 134. Figs. 38. Price 36s.

This book, a companion volume to Dr. Spurling's well-known "Lesions of the Lumbar Intervertebral Disk," is a short and readable account of the main features of the anatomy of the cervical spine in relation to the intervertebral disks, their spontaneous rupture and degeneration, the resulting symptoms and their treatment. The general medical reader will find it useful, but it lacks an adequate recognition of the complexity of the factors producing the neurological symptoms, and of the varied symptomatology of the cervical radiculomyelopathy. Few if any neurologists or neurosurgeons in this country will be likely to agree with the author that "the presence of a severe neurologic deficit . . . furnishes a positive indication for immediate surgical intervention."

Sindromes neurologicós en las malformaciones y lesiones degenerativas del estuchi craneovertebral y su tratamiento neuroquirugico. By S. OBRADOR, P. ALBERT, J. V. ANASTASIO, M. ARRAZOLA, J. R. BOIXADÓS, J. SANCHEZ JUAN and J. J. VÁZQUEZ AÑÓN. Editorial Paz Montalvo, Madrid. 1956. Pp. 341. Figs 152. Price not stated.

This is a comprehensive survey in Spanish of the neurological manifestations of congenital abnormalities and degenerative disorders of the bones of the cranial cavity, the spinal canal, and their lining membranes. The chapters on malformations of the occipito-cervical region, herniation of cervical intervertebral disks, and cervical spondylosis are well-balanced and useful reviews of these topics, including their treatment.

W. RUSSELL BRAIN.

NEUROCHEMISTRY

Neurochemistry. Edited by SAUL R. KOREY and JOHN I. NURNBERGER. 1956. Pp. 244. 29 figures. London: Cassell & Co. Ltd. Price 50s.

The title of this book does inadequate justice to its contents. The term neurochemistry is a recent addition to our accepted scientific vocabulary. In some ways it is an unfortunate term, but evidently it has come to stay. This book, however, is not a mere compilation, as its title might imply, of facts concerning the chemical make-up of the nervous system. It provides instead a series of stimulating essays illustrating well how neurology has now advanced beyond its earlier stages of the description and classification of syndromes to a stage of fruitful analysis of the biochemical disorders that

underlie or are associated with several of the important diseases of the nervous system. It is interesting to note that many of these essays were written not by biochemists who have invaded the field of neurology, but by physicians who have equipped themselves with a knowledge of modern biochemical techniques adequate to enable them to study the pathology of nervous disease.

In general the essays are not comprehensive reviews of different broad fields of work, but rather accounts of different problems now under active development. They range from such relatively chemical topics as the isolation of sphingosine from brain by reversed phase partition chromatography (J. B. Wittenberg), the structure of nucleic acid (A. Rich), and studies on acetal phospholipids (S. R. Korey), to almost purely physiological problems such as the relationship of structure and function in the neurone (S. L. Palay), the relation of cerebral circulation and metabolism to mental activity (L. Sokoloff), and the cerebral metabolic rate in children (C. Kennedy).

The important recent advances in our understanding of the abnormality of copper metabolism that occurs in Wilson's disease are well described in two essays by Huntington Porter and J. Folchi-Pi and by I. H. Scheinberg. A clear and stimulating account of the recent work, largely carried out by the Montreal workers, on the neurochemistry of seizures is given by D. B. Tower.

Other essays on the role of adaptive enzyme formation in morphogenesis (M. W. Gordon), on the action of drugs on the acetylcholine "receptor" (I. B. Wilson and M. Altamirano), and on the relation of proteolipid chemistry to the problem of allergic encephalomyelitis (N. P. Goldstein and M. W. Kies) are also of general biological and medical interest.

The book is attractively printed and produced, and provides stimulating reading as well as a useful bibliography for both the clinician and the biochemist.

R. H. S. THOMPSON.

PSYCHOPHARMACOLOGY

Psychopharmacology. Edited by NATHAN S. KLINE. Publication No. 42 of the American Association for the advancement of Science, Washington D.C. 1956. Pp. 175. 3 figures. Price 32s.

Lysergic Acid Diethylamide and Mescaline in Experimental Psychiatry. LOUIS CHOLDEN, M.D., Editor. New York and London. 1956. Pp. 85. Price $3.00.

Journal of Nervous and Mental Disease—Special Issue—Society of Biological Psychiatry. 10th Annual Meeting, June 1955. Vol. 122, No. 5, November 1955.

These three publications can be reviewed together because they represent recent trends in pharmacology as applied to psychiatry in U.S.A.

The first book, edited by Kline, who has done outstanding work in this field, presents a series of papers read at a conference held in December 1954. It consists of six papers on the clinical application of chlorpromazine and reserpine in psychiatry, two papers on the pharmacology and possible cerebral

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action of these and related drugs, and two papers on the biochemistry of mescaline, lysergic acid diethylamide (LSD 25) and associated compounds. Discussions following the papers are included.

The purpose of the second book, edited by Cholden, is to give the reader a broad survey of some current thinking and problems relating to LSD 25 and mescaline in experimental psychiatry. It reports the proceedings of a round table conference held by the American Psychiatric Association in May 1955. It contains not only the contributions of a wide panel of experts, but verbatim accounts of the discussions, questions and answers that followed. The papers range from a description by Aldous Huxley of his personal experience under mescaline, to the brain effects of LSD 25 in animals.

The special issue of the *Journal of Nervous and Mental Disease* deals almost exclusively with the same topics. Its content includes a few reports on clinical trials only, but a number of important laboratory studies. Moreover, the prospects of the new approach are analysed comprehensively in an opening address by Himwich and in a concluding summary on "Drugs Affecting Behaviour" by Rinkel.

How is one to judge this new way of dealing with a recent development in medicine by conferences each of which leads to a publication in form of a book or pamphlet? After reading the first book one has certainly the feeling that both the conference and its publication are overdone. Much of the material is in the form of preliminary communications in an undigested state. Most of the investigations lack adequate controls for scientific validity and conclusions are of the most tentative nature. With rapid developments in this field much of the information is inevitably out of date before publication. The main value would seem to lie rather in the questions raised than those answered.

In the second book, the various contributions are so wide in their dimensions that it is little wonder that the book lacks cohesion and is not easily digestible. While to bring together so many divergent viewpoints may be a good thing, one is left with the feeling that the conference and book would have achieved more if the terms of reference had been more clearly defined.

The special issue of the *Journal of Nervous and Mental Disease* is more carefully conceived in its selection of articles, although not entirely free from preliminary material that may prove expandable in a short time. The surveying articles in the number are as reticent and critical as one would expect from the authors who can look back at considerable experience in this field.

If one can free oneself from the old-world idea that the content of a book is something of value for posterity, and think of these publications as journalistic records for the day, not intended to survive the present phase, one is impressed by the widespread and intense interest in the problems. Not only clinicians, but workers in the various branches of basic sciences, biochemists, neurophysiologists, pharmacologists and psychologists have vigorously taken up the subject and their collaboration must in the end have an impact on the development of exact methods in psychiatry.

W. MAYER-GROSS.

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A Textbook of Psychiatry. By Sir DAVID HENDERSON and the late R. D. GILLESPIE with the assistance of IVOR R. C. BATCHELOR. 8th Edition. 1956. Pp. xii + 746. London: Oxford University Press. Price 35s.

When this textbook was first published in 1927 it had few rivals; and absence of competition in the matter of textbooks of psychiatry obtained for a number of years. It is therefore right and proper that it should try to retain its popularity by being brought up to date, a task which has been successfully accomplished with the help of Sir David Henderson's new collaborator, Dr. Batchelor.

Textbooks are inevitably hard to evaluate and criticize; for very few people, apart from candidates for examinations, would sit down and read one from cover to cover. What is the function of a textbook then? Should it be a reliable work of reference, in which case a textbook of psychiatry would have to be as lengthy and long-winded as those published on the Continent, especially in Germany? Should it be entirely factual or express the views of the author or authors? In any case, a reviewer should resist the temptation of criticizing a book for what it is not and should content himself with—not too captiously—pointing out any failings in what is presumably intended.

This book, it will be remembered, was intended to present psychiatry from the point of view of the late Adolf Meyer, to whom it was dedicated; for Adolf Meyer wrote very little himself and certainly never penned any textbook. As things are in psychiatry, any textbook is likely to be tendentious; and this book has remained unashamedly Meyerian together with a predilection for psychoanalytical interpretations when it comes to psychopathology.

This brings one to the book's chief weakness—the section on the psychoneuroses. It is not only inadequate from the descriptive point of view, but singularly unhelpful in the matter of treatment, especially psychotherapy; the index, too, is very incomplete.

Nevertheless, both the authors and the publishers are to be congratulated on the publication of the eighth edition of this well-established work which should be as popular as previous editions have been.

The nice typography and gaiety of the dust cover are to be commended!

E. B. STRAUSS.

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SHERRINGTON CENTENARY

THIS is the centenary year of the birth of Sir Charles Scott Sherrington, O.M., a founder and main architect of the physiology of the nervous system. The Royal Society of Medicine, wishing to pay tribute to his life and work, proposes to raise a fund towards a Sherrington Lecture, for the furtherance of knowledge on the nervous system, to be delivered from time to time in the Society's rooms in London.

It is felt that many will wish to contribute: both those who were his friends, pupils and colleagues, and those, more numerous, who, as patients, doctors and scientists, have benefited indirectly from his work.

We wish to take this opportunity to commend the endeavour of the Royal Society of Medicine to establish this memorial to a great pioneer in scientific medicine.

Donations should be made payable to the Secretary, The Royal Society of Medicine, 1 Wimpole Street, London, W.1, and cheques crossed "Sherrington Memorial."

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Foreign Secretary, Physiological Society

PROFESSOR JOHN FULTON, M.D.
Stirling Professor of the History of Medicine, Yale University

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Waynflete Professor of Physiology, University of Oxford

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President, Association of British Neurologists

SIR FRANCIS WALSHE, M.D., F.R.S.
Chairman, Sherrington Memorial Committee, Royal Society of Medicine

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